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REVIEW

Photodynamic Therapy

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Photodynamic therapy (PDT) is an innovative approach to the local ablation of malignant tumours. It has attracted a great deal of interest as a possible means of selectively destroying small cancers. The concept is simple:

> "A photosensitising drug is given intravenously and over the subsequent few days this is retained selectively in the tumour area while it is lost from adjacent normal tissue. Light at a specific wavelength corresponding to an absorption peak of the photosensitiser is then used to activate this drug to produce local necrosis in the tumour and leave the adjacent normal tissue undamaged."

Unfortunately this is rather an optimistic oversimplification. It is extremely difficult to produce truly selective tumour necrosis with PDT based on selective uptake of the sensitiser, and this can only be done under special circumstances with careful manipulation of all of the treatment parameters involved. Under the conditions described in virtually every published paper on PDT, if tumour and normal areas are exposed to the same light dose, there is damage to both (Barr *et al.*, 1990). However, it is now becoming apparent that the *nature* of the biological effects of PDT on normal and malignant tissues is different from that produced by other forms of local injury such as thermal coagulation or ionising radiation. For example, tissue architecture and tensile strength are much better preserved after PDT than after thermal injury as PDT has little effect on collagen whereas heat destroys it (Barr *et al.*, 1987). In the treatment of human disease, understanding and exploitation of these differences are likely to be more important than trying to limit effects to tumour areas. Even though normal tissue may be damaged along with the tumour, if this heals by regeneration of normal tissue, as seems to be the case after PDT, then the net effect is selective eradication of the tumour.

Historical Perspective

The first clinical use of PDT was in 1903, when von Tappeiner and Jesionek treated skin tumours with topical eosin followed by exposure to white light, and the technique has slowly evolved since then. The photosensitisers that have been used for essentially all clinical PDT to date are haematoporphyrin derivative (HpD) or dihaematoporphyrin ether/ester (DHE), which is a more purified preparation of HpD (Dougherty *et al.*, 1983). However, both HpD and DHE are far from ideal photosensitisers as they are incompletely defined mixtures of porphyrins whose composition and stability between preparations varies, and which are difficult to assay. Several promising new groups of drugs are being developed, especially the phthalocyanines, which have similar biological properties to the porphyrins but are easier to handle chemically and assay in tissue and have much more suitable light absorption spectra (Bown *et al.*, 1986). However, these are not yet ready for clinical trials.

Lipson *et al.* (1961) showed that HpD seemed to have an affinity for malignant tumours in man. Later they treated a patient with recurrent breast cancer using filtered red light from a xenon arc lamp, with apparent resolution of visible disease. It was not until 1975 that the potential of PDT in bladder carcinoma was demonstrated by Kelly and Snell. They subsequently gave HpD to 11 patients and looked at tissue fluorescence under ultraviolet

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light, noting a good correlation between areas of tumour and the observed fluorescence, particularly for carcinoma *in situ* (Kelly and Snell, 1976), a finding confirmed by Benson (1986). One patient had an area of bladder illuminated by a mercury vapour lamp transmitted through a rigid quartz rod. Several papillary tumours were necrosed but the authors commented that improved techniques for illumination were needed. Early work with PDT therefore was largely confined to skin lesions until the development of suitable lasers and fibreoptics.

Mechanism of Action

In tissue, the photosensitiser is activated by absorbing light. One of 3 competing processes can then occur (Fig.).

(i) The activated photosensitiser molecules can react with tissue oxygen to produce singlet oxygen, which is thought to be the cytotoxic agent (Dougherty *et al.*, 1983). This is a threshold effect and a certain quantity of singlet oxygen must be produced before a cell is killed. The photosensitiser molecules then return to the ground state and can be activated again.

(ii) The activated molecules can fluoresce (emit light) and then return directly to the ground state, whereupon they can be activated again.

(iii) The activated molecules can go through a different process in which they are destroyed by the same activating light (photodegradation). This means that the total quantity of photosensitiser in tissue is steadily reduced as the tissue is exposed to light. This has important implications for protecting tissues with low concentrations of photosensitiser, as will be discussed below.

Many studies have confirmed this direct cellular toxicity on a wide range of normal and neoplastic cells *in vitro* (with no real difference in susceptibility between normal and neoplastic cell lines), but *in vivo* the most obvious early effect of PDT is to shut down small blood vessels. Endothelial cells are probably affected first, although it is not yet clear how this leads to the vasoconstriction and closing of vessels that have been observed experimentally in both normal and tumour tissue (Star *et al.*, 1986). Studies on the distribution of photosensitisers in animal tumour models demonstrate that the relatively small degree of selectivity of uptake of photosensitisers that is seen in tumours is due to their retention in the vascular stroma (Bugelski *et al.*, 1981). At a cellular level *in vivo*, as with the *in vitro* studies, there is no difference in uptake between malignant cells and the normal cells from which the malignancy arose.

Light and Lasers

The main requirement for the therapeutic light is that the wavelength used should match an absorption peak of the photosensitiser. In addition, the depth of tumour that can be treated by PDT below the illuminated tissue surface is largely limited by the depth to which light will adequately penetrate that tissue. The most penetrating wavelengths to use are in the red and near infrared part of the spectrum, but even using these, the maximum depth of necrosis possible in most tissues is typically no more than about 5 mm. For this reason, PDT is best for small tumours, although larger lesions can be treated by inserting the laser fibre directly into the target tissue. HpD and DHE both have only a

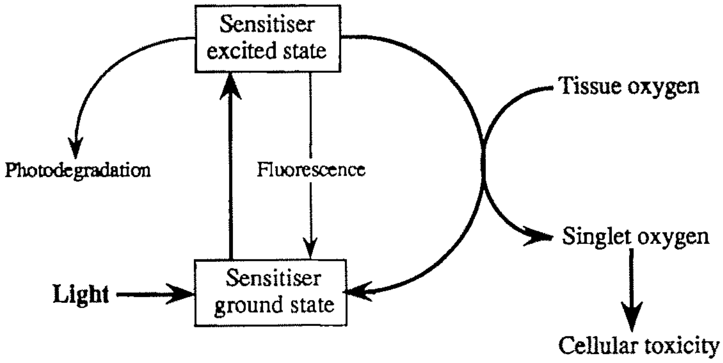

Fig. Outline mechanism of photodynamic action. Light energy absorbed by the photosensitiser molecules elevates them to an excited state. This is short-lived and can react to produce singlet oxygen which is highly toxic and causes local cell death Some of the excited photosensitiser molecules may decay back to the ground state by emitting light (fluorescence) or may become irreversibly degraded minor absorption peak for red light (at 630 nm), although newer sensitisers generally have their major absorption bands at longer wavelengths for greater tissue penetration (*e.g.* aluminium sulphonated phthalocyanine at 675 nm, benzoporphyrin at 700 nm and silicon naphthalcyanine at 776 nm).

Laser light is not an absolute requirement for PDT but is just a convenient way of producing high intensity light at exactly the right wavelength in a small enough beam to be focused into a thin optical fibre for endoscopic use. At present, the most suitable laser sources are argon pumped dye lasers or copper vapour pumped dye lasers, as the wavelength of the output beam can be tuned to match the absorption peak of the photosensitiser being used. The gold vapour laser emits at 628 nm, which is exactly right to excite HpD and DHE but would not be suitable for the newer sensitisers. Other possibilities include pumping dye lasers with excimer and frequency-doubled neodymium: YAG lasers. Over the next few years much cheaper, more compact and reliable semi-conductor lasers are likely to become available for use with sensitisers that absorb at the longer wavelengths, but it is only very recently that their specifications have started to come close to those required for PDT.

Clinical Applications

The bladder seems ideally suited to PDT as it is readily accessible and the entire mucosa can be treated simultaneously. Resistant superficial bladder cancer is usually multifocal, and areas of occult dysplasia and carcinoma *in situ* (Cis) do not have to be precisely defined for PDT to be effective. Advances in ureteric instrumentation and light delivery systems make upper tract urothelial tumours theoretically treatable. There is also the important consideration that these superficial lesions lie well within the depth of tissue easily treated by PDT.

The other 2 important hollow organs in which PDT may have a useful role to play in tumour therapy are the gastrointestinal tract and the airways, although tumours in these organs are usually much larger than those in the bladder at the time of presentation. It is seldom appropriate to use PDT alone for these tumours unless they are small but it may be of value as adjuvant therapy if the main bulk is removed by other techniques. For solid organs such as the prostate, light can be delivered to the target area by interstitial fibres but the volume treated around each fibre site is small. In general, therefore, multiple fibres would be required and such applications are still in the preclinical phase (Pantelides *et al.*, 1990). There are numerous clinical studies showing anecdotal success with PDT for tumours of the skin, head and neck and brain, although as yet no controlled trials.

Clinical Results in Bladder Cancer

There are several reported series of PDT in bladder cancer that give an average "complete response" rate at 3 months of about 65% (Table). This implies the disappearance of all visible tumour and, where available, negative biopsies and urine cytology. Differing selection criteria, tumour pathology and treatment parameters make direct comparison difficult but there is a consensus that PDT is most effective at treating Cis, less effective for superficial papillary disease, and ineffective for invasive tumour. The best results are those of Benson (1986, 1988), who reported 27 patients with resistant Cis who refused cystectomy; 23 of these (85%) showed a complete response to PDT but the other 4 had coexistent papillary tumour which persisted, although their Cis responded. Conversely, Prout *et al.* (1987) reported on 19 patients, the majority of whom had papillary bladder cancer alone, and found that only 47% had a complete response. The only British series so far reported (Williams and Stamp, 1988; Stamp *et al.*, 1990) comprised 10 patients with multiple superficial bladder tumours (Cis, Ta and T1) that had not responded to intravesical chemotherapy. A complete initial response was seen in 4 patients and a partial response in another 4. Only 2 patients remained tumour-free (in excess of 2 years) and 7 ultimately developed an invasive cancer, of whom 2 died.

There are few other published data on the durability of the response of bladder tumours to PDT to suggest whether or not PDT offers any worthwhile improvement in either recurrence rate, time to progression or survival. Benson (1988) reported a 50% recurrence of focally treated Cis at 1 year, though most recurrence was in previously uninvolved areas and was successfully re-treated with PDT. Jocham *et al.* (1989) reported that 9 of 15 patients with Cis remained clear with follow-up in excess of 2 years after whole bladder PDT; 2 became clear with a second treatment and 4 had recurrences after a mean of 20 months.

Complications Following PDT to the Bladder

At first sight these results seem impressive, especially as they have been achieved largely in patients

Table Results of Photodynamic Therapy in Bladder Carcinoma

					Response at 3 months	
Authors	*No. of patients*	*Sensitiser (mg/kg)*	*Interval to treatment (h)*	*Light dose (J/cm²)*	*Complete*	*Persistent tumour*
Benson	15	HpD	3, 48 or both	150 (F)*	15	0
(1986)	12	(2.5–5)	3 or 48	25–45 (WB)*	8	4
Harty *et al*	2	DHE	72	25 (WB)	1	1
(1989)	5	(2)		25 (WB) + 100 (F)	4	1
Hisazumi *et al.*	9	HpD	48–72	120–250 (F)	5	4
(1983, 1984)	2	(2–3.2)	48	10 (WB)	2	0
Jocham *et al*	15	DHE/HpD	40–72	35 (15–70) (WB)	11	4
(1989)		(2–3)				
Nseyo *et al.*	11	DHE	72	10–60 (WB)	3	8
(1987)	10	(2)		100–200 (F) + 5–60 (WB)	4	6
	2			100–200 (F)	0	2
Prout *et al*	17	DHE	48	100–200 (F)	8	9
(1987)	2	(2)		5.5–10 (WB)	1	1
Shumaker and Hetzel (1987)	13	DHE (2)	72	25 (WB)	12	1
Tsuchiya *et al.*	8	HpD	48–72	120–360 (F)	8	0
(1983)		(2.5)				
Williams and Stamp	10	DHE	72	10–15 (WB)	4	6
(1988)		(2)				
Total	133 (100%)				86 (65%)	47 (35%)

*Denotes focal or whole bladder treatment.

who have failed all other modalities of treatment short of cystectomy. However, the complication rate was alarming, as will now be discussed.

Functional impairment. Most authors state that their patients develop irritative symptoms following PDT but these are often described as "transient" and of no particular worry. There has almost certainly been a gross under-reporting of side effects by the enthusiasts of PDT, often no doubt because they have not been specifically sought, and many patients would have had some pre-existing symptoms anyway. All authors who did look specifically at bladder function after PDT found serious impairment in a high percentage of patients. Nseyo *et al.* (1985) reported severe side effects in all of an initial series of 6 patients undergoing whole bladder PDT. Two patients had such a marked reduction in bladder capacity with incontinence that they required a cystectomy for these PDT-induced symptoms alone, although their bladders were found to be clear of tumour. Following animal experiments they recommended treatment parameters which produced better results in a subsequent 15 patients, with on average only a 20% reduction in bladder capacity which recovered within 3 months (Nseyo *et al.*, 1987). However, the Sheffield group (Williams and Stamp, 1988; Stamp *et al.*, 1990), using these supposedly improved parameters, still found severe dysuria and reduced bladder capacity in all of their patients. Some were hospitalised for several weeks and 1 patient was left with a bladder capacity of only 50 ml after voiding a sloughed "cast" of bladder mucosa. Jocham *et al.* (1989) reported a reduction in bladder capacity in some of their patients in excess of 50% and 3 still had a 70% reduction 1 year after PDT. Some authors have suggested not giving PDT to patients who have a pre-treatment bladder capacity less than 150 ml (quite common) or who have received radiotherapy (rare for superficial tumours) as they seem to have the worst complications.

Upper tract complications. Both ureteric reflux and ureteric obstruction were seen in the initial series of Nseyo *et al.* (1985) but in general no problems with the upper tracts have been mentioned by other authors until a recent report by Harty *et al.* (1989) in which they studied the side effects after PDT in a series of 7 patients who were given whole bladder treatment. Five patients had a significant reduction in bladder capacity after PDT which persisted at 1 year in 4 of them. Deep bladder biopsies showed marked fibrosis in the muscle layer. These 4 patients also developed persistent bilateral hydronephrosis and grade 4 vesicoureteric reflux. It is interesting that the 1 patient in this series who escaped these problems still had a complete response; he had received only two-thirds of the intended dose of DHE.

Cutaneous photosensitivity. Any drug given systemically will be distributed throughout the body and so it is inevitable that photosensitisers will be taken up to some extent in the skin. Unfortunately, HpD and DHE absorb light well throughout the range of wavelengths in sunlight, which means that patients may develop cutaneous photosensitivity to ambient light. This may last several weeks and require the patient to remain in subdued lighting and to wear protective clothing. This is a major factor against patient tolerance of PDT with these sensitisers and despite warnings, most series report a small number of patients who develop significant sunburn. Other ways of administering photosensitisers have been tried with the aim of avoiding skin sensitivity. Direct intra-tumour injection is suitable only for solitary bladder tumours (Amano *et al.*, 1988) and would clearly not be feasible for Cis. Intravesical administration of HpD has not been successful (Benson, 1988) and our studies on the intravesical uptake of phthalocyanine show that although significant amounts are absorbed by normal bladder, the uptake is patchy and unpredictable (Pope *et al.*, 1990).

The most likely solution lies in newer photosensitisers which, although still given intravenously, are either cleared more rapidly from the skin or, like the phthalocyanines, have a localised absorption peak at a longer wavelength than HpD, away from the main concentration of solar emission, which produces much less of a skin reaction (Tralau *et al.*, 1989). Using a phthalocyanine sensitiser at low dose levels, the problem of cutaneous sensitivity to sunlight is likely to be virtually eliminated. Another approach may be to use singlet oxygen quenchers which can be given after PDT to reduce skin sensitivity in animals, though their clinical efficacy is not yet proven (Dillon *et al.*, 1988).

With so many serious problems it is perhaps surprising that anyone is still trying to use PDT in the bladder. Several of the clinical pioneers did decide to stop clinical work and go back to the laboratory to try and solve the problems (Nseyo *et al.*, 1985, 1988; Reed *et al.*, 1989). However, even now, a survey of the literature in this field shows that there is a remarkable absence of basic studies on exactly what PDT does to normal and neoplastic tissue in the bladder. There are very little background data on which to base the light and sensitiser doses used clinically, and the values that have been used must be regarded as little more than inspired guesses. This is illustrated by the wide range of values used for the most important treatment parameters given in published clinical series of PDT for superficial bladder cancer (Table):

Sensitiser dose:	HpD 2–5 mg/kg DHA 2 mg/kg (all authors)	
Time between sensitisation and light exposure: 3–72 h		
Light dose:	whole bladder	5–70 J/cm^2
	focal treatment	100–360 J/cm^2

As has happened on many occasions in the history of medicine, the clinicians have tried to run before their scientific collagues had taught them to walk! Often this empirical approach has worked, but for PDT in the bladder, clearly it has not. Phase III clinical trials of PDT for bladder cancer are under way in several countries both for resistant Cis and as prophylaxis against recurrent papillary disease. There must, however, be some doubt about whether these trials are appropriate in our current state of knowledge, since the parameters being used are essentially the same as those that have produced irreversible damage to bladder muscle in many of the patients treated over the last few years.

Selectivity of PDT

The side effects of PDT on the bladder outlined above appear to be the result of necrosis followed by fibrosis in the muscle layer of the bladder, *i.e.* the result of damage to normal tissue rather than to tumour. Much of the attention focused on PDT stems from the possibility of selective destruction of malignant tumours, but these results must make us ask how much selectivity there really is under the conditions being used at present. Also, bearing in mind the pathology we are trying to treat, should we be looking for selectivity between the superficial and deep layers of the normal bladder wall rather than between normal and neoplastic areas? Much of the experimental work on PDT has stressed the importance of selective uptake of photosensitisers using tumours transplanted subcutaneously in mice and rats compared with the adjacent skin and muscle. However, what is important clinically is the difference in uptake or retention between a tumour and the *adjacent normal tissue in which that tumour arose* (or into which the tumour has spread); it is suprising how little data are available in the world literature on this crucial point. There have been many reports (both clinical and experimental) on selective fluorescence of malignant tumours after porphyrin sensitisation, but this is normally excited by ultraviolet light, which penetrates less than 0.1 mm into tissue, so that one is only looking at surface differences between tumour and normal areas. It is difficult to correlate these measurements with concentrations of photosensitiser in the bulk of the tumour, though these techniques may have a useful role in diagnosing areas of endoscopically occult malignancy (Lin *et al.*, 1984). Work on animal tumours of the colon and pancreas has shown that the best selectivity of uptake achieved with either HpD or aluminium sulphonated phthalocyanine (AlSPc) is only in the order of 2-3:1 between tumour and adjacent normal tissue. The major exception to this is for intracranial gliomas, where the ratio is considerably greater at 28:1, most likely due to the breakdown of the blood brain barrier in tumour areas (Tralau *et al.*, 1987). Little such data are available for bladder tumours.

Any form of local treatment has some degree of selectivity. Therapy with ionising radiation or with a thermal laser such as the neodymium: YAG will produce the greatest effect in the area that receives the highest dose. If the light used for PDT is directed solely at tumour tissue, then naturally necrosis is confined to the tumour area. Much higher degrees of selectivity are possible by controlling where the light is directed than can be achieved solely by differences in the uptake of the sensitiser between normal and neoplastic areas. For bladder Cis, however, we are dealing with a situation when one cannot localise all neoplastic areas precisely and both normal and tumour areas will be exposed to similar light doses. The understanding of the nature and healing of PDT damage to normal tissue is therefore fundamental to the establishment of those treatment parameters which will eradicate tumour but not cause irreversible damage to normal tissue.

Experimental Studies on Normal Bladder

The first objective in planning PDT experiments on the bladder must be to decide what biological effect is desired and then to manipulate all of the parameters involved to see if this effect is achievable. It is surprising that so little has been done along these lines.

The clinical reports described above have shown that the main problem is scarring in the muscle causing irreversible changes to bladder function. In whole bladder treatments, no-one has shown necrosis limited to the tumour areas, and instead large areas of mucosa have sloughed which must be presumed to include both normal and neoplastic regions. These have healed with regeneration of normal mucosa which for patients with Cis means that their tumour has been eradicated. Thus it seems less important to attempt any form of selectivity between normal and abnormal mucosa, but highly appropriate to try to limit the damage to the mucosa and submucosa and leave the muscle intact. Experiments designed to answer this question can be carried out on normal animals, which is much simpler than finding an adequate animal model of *in situ* bladder cancer.

Two sets of parameters can be manipulated: those related to the photosensitising drug (*e.g.* dose, route of administration and time between sensitisation and light exposure) and those related to the light (wavelength, power, exposure time and geometry of light distribution).

The first consideration for the sensitiser is how it is distributed. For localisation within different layers of the bladder wall the best technique is fluorescence microscopy. In experiments using AlSPc as the sensitiser, immediately after intravenous administration, similar concentrations are found in all layers. However, after 24 to 48 h there is 3 to 4 times as much photosensitiser in normal mucosa and submucosa as in the underlying muscle; this is due to more rapid clearance from the muscle layers and seems the best time interval to use (Pope *et al.*, 1990). Experiments on other tissues (particularly the colon) have established that there is a threshold level for the tissue concentration of photosensitiser at the time of light exposure below which insufficient singlet oxygen is generated to cause tissue damage, even in the presence of excess light (Barr *et al.*, 1990). This is because the sensitiser is destroyed by photodegradation (photobleaching).

Putting both these results together, it would be expected that if the tissue concentration of photosensitiser was below the threshold in muscle but above it in the mucosa and submucosa, then there might be a mechanism for limiting PDT effects to the superficial layers. This approach has the added attraction that as the sensitiser is photobleached out of the muscle layer, no PDT damage should be produced however high the light dose. Experiments confirm that with a low dose of AlSPc (0.5 mg/kg in the rat, 24 h prior to light exposure), damage can be limited to the superficial layers in a way that is independent of the light dose, the only requirements being that sufficient light is delivered to every point on the bladder surface and that the fluence rate is not high enough to cause thermal effects. Urodynamic studies on rat bladders at a range of times from a few days to 3 months after PDT indicate that if necrosis can be restricted to the mucosa and submucosa, then the subsequent reduction in compliance and capacity during the healing period is less, lasts a shorter time and is more completely reversible than when the muscle layers are also damaged (Pope and Bown, 1991). It is not possible to avoid initial side effects completely because there is a marked inflammatory response where the mucosa sloughs, but if these results can be extrapolated to man they should reduce the complications to an acceptable level and there should be little permanent reduction in compliance or capacity.

Few other workers have studied the effect of PDT on bladder function in an experimental model. Nseyo *et al.* (1988) looked at the effect of varying light dose and filling pressure during PDT on the canine bladder, which they had previously found to be relatively resistant to PDT. Although they did not see any permanent reduction of bladder capacity in surviving animals, higher filling pressures produced a more delayed recovery and were associated with greater muscle damage (thinning of the bladder wall during overdistension may well extend the expected depth of damage). They did not alter the sensitiser dose (well above threshold), so not surprisingly higher light doses produced more long-term damage than lower ones, though the small numbers of animals studied precluded any assessment of the acute histological effects, particularly as to whether a clinically appropriate degree of photodynamic damage had been achieved.

Light Delivery and Dosimetry

At the photosensitiser concentrations commonly used clinically, the light dose seems critical. However, it is not easy to calculate accurately the dose absorbed by the mucosa. The problem of achieving an even light distribution has been approached in several ways. Some workers have filled the bladder with a diffusing medium such as dilute intralipid and used a special positioning catheter to centre the laser fibre (Jocham *et al.*, 1989). Others have developed ingenious mechanical rotating devices for stepwise illumination of the entire bladder mucosa (Hisazumi *et al.*, 1984). Most authors have used some type of bulb tip diffusing fibre (Benson, 1986) centred as accurately as possible within the bladder and accepted that the light distribution will not be entirely even, particularly around the bladder neck. Multiple isotropic detectors placed in close proximity to the bladder wall can be used to monitor the incident light and, since there is a high internal reflectance from the bladder wall, it may be important to measure this light rather than just the fluence of the primary beam emitted from the fibre tip (Marynissen *et al.*, 1989).

All of these methods require considerable enthusiasm and patience to use, so that simplification of light delivery would make PDT easier to perform. One way of doing this, as mentioned already, is by using the photobleaching which occurs at low sensitiser concentrations. Under these conditions it may not be necessary to deliver a precise light dose to every part of the bladder, but merely a minimum effective dose to all points, with no limit to the maximum at any point. Therefore some of the difficult problems associated with the accurate calculation and even distribution of light over the entire bladder mucosa would become less important, although the high total light doses needed may require long treatment times with currently available laser systems.

An alternative approach to the problem of avoiding unwanted PDT damage in the muscle layers of the bladder is to activate the photosensitiser with a wavelength of light less penetrating than the red light (630 nm) used in all clinical studies with HpD and DHE. Green light would be expected to penetrate the bladder wall only 1 to 2 mm and HpD has a strong absorption peak in the green spectrum (at 507 nm). Haemoglobin also absorbs strongly here, however, so that any surface bleeding may shield underlying tumour and the reduced internal reflection of green light within the bladder will make dosimetry more difficult. There are no published clinical data as yet using green light to address these points. Activation with green light is not possible for the phthalocyanines and most of the newer photosensitisers under study, which absorb only in the red part of the visible spectrum. Green light would also not be suitable for any other clinical application of PDT apart from bladder Cis.

Photodynamic therapy has been studied by many research groups world-wide with numerous claims made for its efficacy over a period of more than 10 years. It would seem to hold particular promise for treating various types of superficial bladder cancer, especially resistant Cis. Why then is it not yet an established treatment? The main reason is that clinical PDT, as with many new medical treatments, has evolved on a largely empirical basis whilst fundamental questions regarding its mechanism of action and optimum treatment parameters remain unanswered. It is not surprising, therefore, that few publications give convincing evidence of clinical efficacy for the management of Cis, or indeed for most other conditions for which it has been tried, and some serious complications have been reported. The development of an irritable contracted bladder, or upper tract damage secondary to ureteric obstruction or reflux, are tragic sequelae for a patient in whom PDT has successfully eradicated resistant and potentially lethal carcinoma. One does wonder if more experimental studies *prior* to the clinical application of PDT in the bladder could have reduced the incidence of these complications.

We believe that PDT has great potential in urological oncology, although the clinical results achieved so far have not been satisfactory. PDT is a topic that requires expertise in a range of both clinical and basic science fields and few people have a wide enough spectrum of knowledge to realise which are the most critical gaps in our knowledge and hence where the research effort should be directed. There is general agreement that light dosimetry is the biggest problem in treating bladder cancer but most workers see uniform illumination of the entire bladder mucosa as the challenge. We suggest that the only requirement for the *light* is that the amount at every point should be above a certain threshold. The real challenge comes in getting the dose of *sensitiser* right, so that PDT effects are limited to the superficial layers of the bladder. This optimum is likely to be much lower than the values currently used clinically. Of course, one must ask what depth of necrosis is required, as when using low sensitiser doses this will be limited but quite adequate to treat Cis.

New sensitisers and more precise ways of delivering them to tumour tissue (*e.g.* incorporated into liposomes or bound to monoclonal antibodies) may be developed but this must be balanced with work designed to establish how the biological principles studied in animals can be applied to treating real cancers in real patients. The clinical use of PDT requires a new way of thinking about treating human disease and it will take much time, effort and high quality data to establish its efficacy. Only careful and logical scientific experiments and rational clinical trials will tell us if photodynamic therapy is really here to stay.

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A User's Guide to Flexible Cystoscopes

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Summary—This survey, carried out on behalf of the BAUS Instruments Committee, aims to assist the urologist in choosing a flexible cystoscope. The 5 most commonly available flexible cystoscopes (from ACMI, Olympus, Pentax, Storz and Wolf) were assessed in a clinical setting for handling, image quality and user satisfaction. Several technical characteristics, including deflection range, irrigant flow rate and optics, were tested in the laboratory. Whilst all instruments were satisfactory, the favourite of our testing panel was the Olympus CYF-2, which also came out best in the technical assessment and has the most comprehensive service support. The cheaper Storz instrument also performed well.

Flexible cystoscopes are becoming increasingly popular for out-patient diagnostic and minor therapeutic manoeuvres (*e.g.* biopsy, stent removal) needing only topical urethral anaesthesia. Although fibreoptic endoscopes have been used in gastroenterology for over 25 years and the first reported use of a flexible instrument to view the bladder came from Japan in 1973 (Tsuchida and Sugawara), it was not until 1982 that any real experience with these instruments was reported by Burchardt.

Not surprisingly, the early flexible cystoscopes were derived from gastroenterological endoscopes, usually choledochoscopes, and were less manoeuvrable and of larger calibre than the present purpose-designed instruments, the first of which was introduced by Olympus in 1986. Flexible cystoscopy is now well established and has been shown to be at least as accurate in diagnosis (Clayman *et al.*, 1984), more efficient in practice (Fowler *et al.*, 1984) and more acceptable to patients than conventional rigid endoscopy (Flannigan *et al.*, 1988). The applications of this technique have been reviewed by Kennedy and Preminger (1988).

Many urologists will consider purchasing a flexible cystoscope and an increasing number of endoscope manufacturers are entering the field. This report, whilst no substitute for personal trial, aims to offer some guidance in selection.

Materials and Methods

The 5 most commonly available flexible cystoscopes in the UK were chosen for this assessment. They were the ACMI AFC-1 (distributed by Cory Bros), the Olympus CYF-2 (Keymed), the Pentax FCY 15P (Pentax, UK), the Storz 11272 (Rimmer Bros) and the Wolf 7305 (Richard Wolf, UK). The more expensive Pentax FCY 15H differs from the FCY 15P in having a connecting lead for automatic flash photography and some minor differences in control layout. The new Storz flexible cystoscope (11275), which is claimed to be improved in several respects, was not available at the time of testing. The instruments tested were demonstration models provided by the distributors and the assessment was in 2 parts.

User test

Each instrument except for Pentax was assessed by the same 5 urologists, with varying prior experience of flexible cystoscopy, on routine check cystoscopy lists. This was a subjective opinion of handling (ease of insertion, controls, manoeuvrability, *etc*) and of image quality. Instruments were then graded by each urologist for overall satisfaction in use. The Pentax cystoscope was tested subsequently in

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Based on a Poster Demonstration at the 46th Annual Meeting of the British Association of Urological Surgeons in Scarborough, July 1990 response to BAUS members' enquiries, though by a different panel. A direct comparison with the other instruments in these respects should therefore not be made.

Technical assessment

This included a measurement of irrigant flow rate (90 cm head) with and without the manufacturer's biopsy forceps in position. Measurements of deflection of the flexible tip were made and by how much this was reduced when using either biopsy forceps or a 400 micron laser fibre. Optical quality, image size and field of view were assessed by photographing a test card in air under standardised conditions using an automatic flash-light source (Storz) and a 35 mm camera (Olympus OM2). The number and density of optical fibres in the visible image were calculated from test negatives using a microscope and graticule eyepiece. The manufacturers' own figures for instrument dimensions were used.

Results

User tests

The Olympus CYF-2 was best liked by our panel in all respects (Fig. 1) and in particular has superior optics. Some found the detachable channel taps awkward to connect. It also has a less urologically orientated range of accessories as standard than the other instruments, *e.g.* no grasping forceps or basket, though others can be ordered separately.

The Storz cystoscope handled well and produced a bright, sharp, though rather smaller image than the other instruments. There were no specific criticisms.

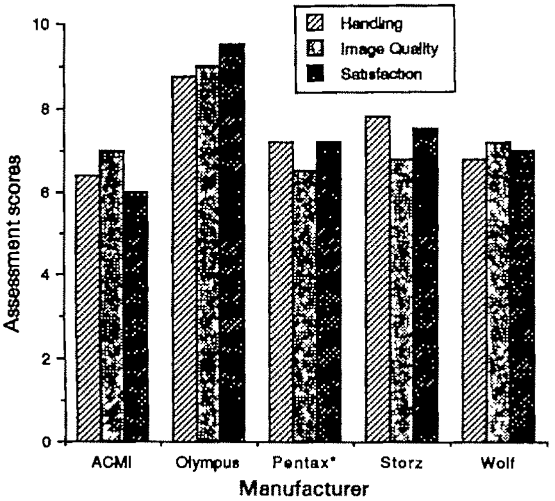

Fig. 1 Average marks awarded (max. 10) for handling, image quality and general satisfaction in use *Pentax tested by different panel from the others.

The Pentax has a couple of features which identify it as a product from a general fibrescope manufacturer. Firstly, it has the same eyepiece as its cousin gastroscopes, bronchoscopes, *etc*, which requires an adaptor to fit general urological accessories. Secondly, the irrigation is controlled by a firm rubber button compared with the more usual tap arrangement (on the FCY 15H a second pressure gives suction). This button proved quite awkward to keep depressed throughout filling, especially when simultaneously manipulating the tip. The irrigation comes in close to the top of the instrument, whereas the aperture for the biopsy channel is lower down in the usual place, a good point though somewhat spoilt by a poorly designed sealing cap. The instrument handled well, though the image was rather small. Like Olympus, it has a poor range of accessories (biopsy forceps only).

Wolf is the only manufacturer to use a standard light lead (all others have an integral lead) and as the light lead is probably the part most prone to damage, a separate one has clear advantages. This also makes the instrument less cumbersome to handle, especially for cleaning and storage, and there are no potential problems with light source compatibilitiy (unlike Olympus). Although light transmission should be better with a continuous bundle, we did not find it deficient in the Wolf, the light source itself being a more important determinant. The main disadvantage with the Wolf was its excessive flexibility, this made it less easy to introduce in the male as it tended to concertina, especially if there was any urethral narrowing, a poorly relaxed distal sphincter or occluding prostate.

The ACMI cystoscope was a sturdy instrument with good optics but was let down by a couple of design features to which one might adapt with frequent use but which were initially off-putting. Deflection was controlled by a large scabbard-like lever, into which the operator's thumb was intended to fit and manipulate by movement at the carpometacarpal joint; this was much more awkward than the thumb tip control used on the others, especially if the handpiece was rotated to any extent. In an attempt to avoid the need to do this, the tip of the ACMI deviated equally in both directions.

Technical tests

All cystoscopes were fairly similar in diameter (between 15.4 and 17 F), though the Pentax and

Wolf were the thinnest. The single instrument and irrigation channel ranged in size from 5 F (Wolf) to 6.9 F (Olympus) and irrigant flow rates from 130 ml/min (ACMI) to 205 ml/min (Olympus) (Table 1). This was greatly reduced with biopsy forceps in place, though part of this variation is due to the manufacturers' differing sizes of forceps. Flow can be improved by injecting irrigant under pressure and ACMI provide a second tap for this. Backflow is insufficient to empty the bladder except by using suction.

The tip of all instruments, apart from the ACMI, would deflect more upwards (range 180–220°) than downwards (range 80–105°) (Fig. 2). The ACMI would deflect similarly in both directions (almost 180°) to avoid the need for rotation of the handpiece. Pentax and Wolf had the greatest range but the latter was also the most restricted by forceps or a laser fibre. This may prevent "recurve" access to lesions near the bladder neck for which a deflection greater than 180° is usually needed. Some manufacturers, particularly Storz, claim a greater deflection range than was measured in our tests. This may have been due to some slackening of the control cables in the particular instrument tested.

The image quality of all instruments was acceptable, though not equivalent to that of a rod lens telescope. The most striking variation was in image size, that of ACMI and Olympus being more than twice the area of the Storz image, though still less than half that of a rod-lens telescope (Fig. 3). The size and granularity of the image is a reflection of the number and density of fibres in the optical bundle, which varied widely (Table 2). The Olympus gave a slightly sharper (*i.e.* less granular) image than the others, with Wolf being the most granular, though image size seemed a more important factor in determining perceived image quality. It can also be seen from Figure 3 that the size and spacing of the fibres are similar in Olympus, Pentax and Storz and it is the large variation in the numbers of fibres that results in the significant differences in image size. Fibres in the Wolf are less closely packed, producing a more granular image, whereas those in the ACMI are arranged in a non-linear pattern. Differences in the angle of view were not noticeable in use, though they are wider than in a rigid telescope, producing more of a "fish-eye" type view.

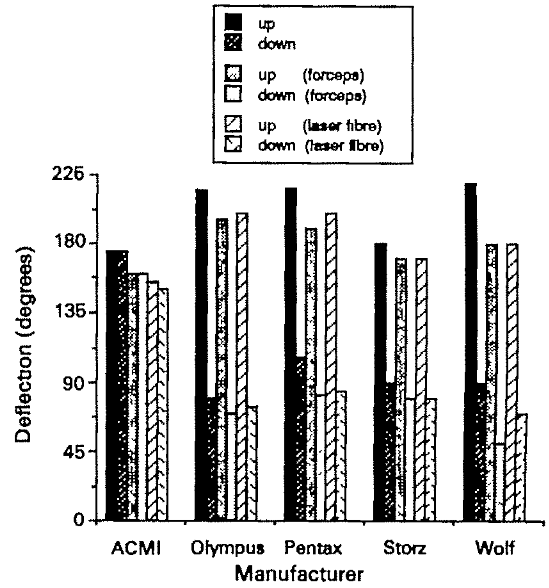

Fig. 2 Comparison of distal tip deflection and reduction in movement range by biopsy forceps or laser fibre

Discussion

All of these instruments are adequate and some of the differences between the instruments brought out in this comparison will be of more practical importance than others. Ease of use is vital, as

Table 1 Instrument Calibres and Irrigant Flow Rates

	ACMI	*Olympus*	*Pentax*	*Storz*	*Wolf*
Calibre (F)					
External	17*	16.6	15.4	15.7	15.5
Working channel	5.5	6.9	6.3	6.3	5.0
Irrigant flow (ml/min)†					
Free	130	205	165	115	175
With forceps‡	30	35	30	55	20

* Bevelled 15 F tip.

† At 90 cm head saline.

‡ Manufacturer's own (calibres vary).

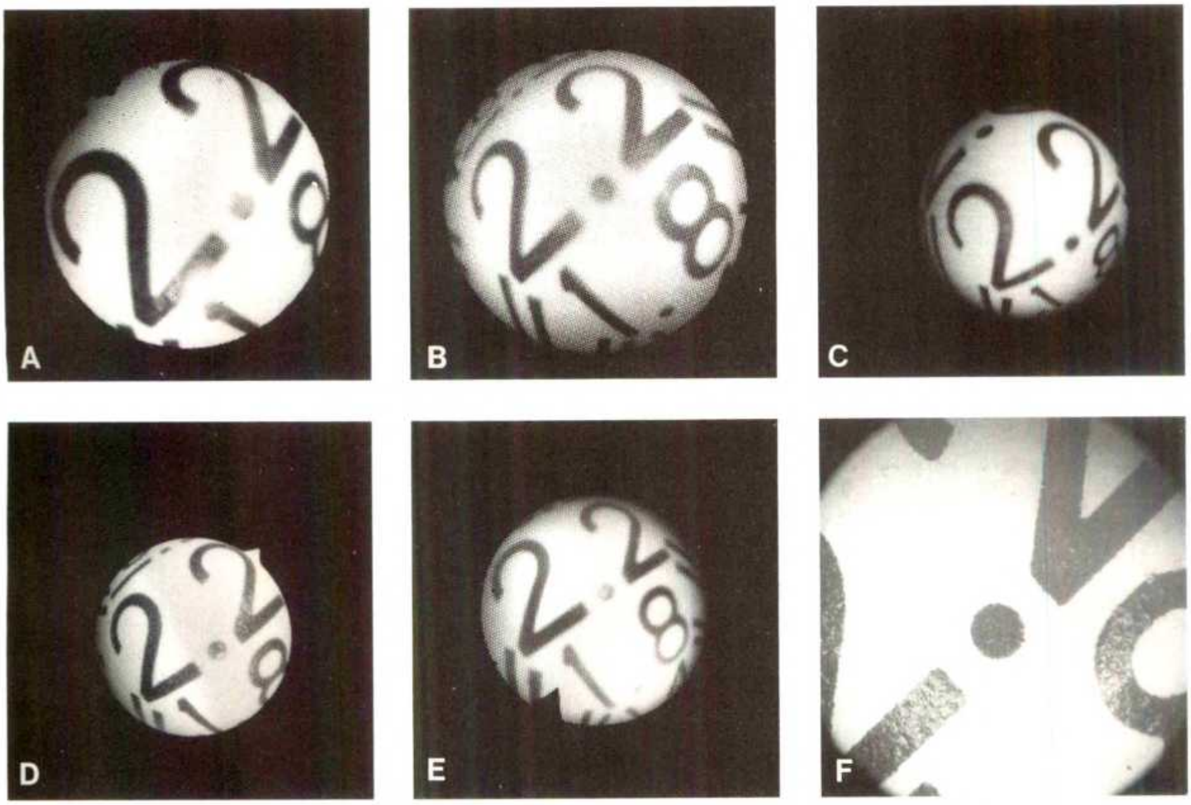

Fig. 3 Test card photographs illustrating the size and fibre orientation of the visible image produced by each instrument. The view obtained under the same conditions using a rod-lens 0° telescope (Storz) is shown for comparison. All photographs are enlarged to the same extent. Note differences in fibre size and layout as well as total numbers. Table 2 summarises these differences. (A) ACMI. (B) Olympus. (C) Pentax. (D) Storz. (E) Wolf. (F) Rod-lens 0° telescope (Storz).

flexible cystoscopy takes some practice, being more akin to gastroscopy than rigid cystoscopy. In this respect Olympus and Storz were the best and the rather different techniques needed to operate the ACMI seemed less satisfactory. In particular, most users felt that uneven deflection combined with rotation of the instrument gave a better view, especially of the bladder neck; it also helped orientation, since one does not instinctively know the position of the distal end. All of our testers felt that the increased difficulty in introducing the very flexible Wolf down the male urethra was a major disadvantage.

Optically, our panel thought that Olympus was the best. This was confirmed in the technical tests, where it produced the largest image from a

Table 2 Characteristics of the Visible Image Bundle

Manufacturer	*Image area** *(cm²)*	*Fibre density** *(fibres/mm²)*	*No. of fibres†*
ACMI	1.8	42	7560
Olympus	2.0	60	12000
Pentax	1.0	56	5600
Storz	0.9	56	5040
Wolf	1.2	33	3960
Rod lens telescope (Storz)	4.1	—	—

* Measurements directly from negatives taken on a 35 mm endoscopic camera with a 140 mm focal length connector.

† In the visible image only, *i.e.* excludes those covered by peripheral masking.

considerably greater number of fibres than its competitors, more than 4 times the number making up the Wolf image (Table 2). Pentax and Storz had a similar layout and size of their optical fibres to Olympus but many fewer, giving an equally sharp but much smaller image. Users of ureteroscopes will be familiar with the smaller image sizes reflecting overall dimensions, but it is interesting that within a similar external diameter the Olympus also has the largest working channel.

A large working channel will increase irrigant flow, although this is unnecessary in most cases, and if the bladder is allowed to fill before the examination is finished it can only be emptied through the instrument using suction. The main advantage of a larger working channel would be to use larger accessories or allow some irrigant flow with, for instance, a laser fibre in position. Both ACMI and Storz provide a comprehensive set of accessories as standard, including biopsy and rat tooth forceps, multi-radiate forceps or a basket for retrieving stents and stone fragments, and a diathermy electrode (standard electrodes are too short) with a bipolar option available from Storz.

If the outer cover of a fibreoptic instrument is breached, *e.g.* by a crack in the rubber over the bending section, or the lining of the working channel is damaged by an accessory and unrecognised, then sterilising solutions may enter and irrevocably damage the optical bundles. There seems no consensus between manufacturers on the need for such "leak testing" and their recommendations vary from testing the whole instrument either underwater with a compressed air source (Olympus) or with a simple hand pump and gauge (Pentax and Storz), to no provision at all (ACMI). The ACMI cystoscope can be gas sterilised, which is not generally practicable in this country, and there is a risk of placing it in sterilising solutions with the vent valve turned to "gas".

Instrument support is important, especially if a single endoscope is critical to the running of an outpatient list. Keymed and Pentax are the only distributors to service and repair their instruments in the UK (which should be much quicker) and the only ones to offer a guarantee that covers accidental damage (not an insignificant risk, especially using lasers, though Pentax are likely to exclude laser damage). This can be extended to a service contract after the first year (approximate annual cost £600). The other distributors all said that they would loan a replacement instrument, *if available*, during absence for repair.

All of these cystoscopes, except Pentax, have standard eyepieces for accepting teaching aids and cameras but the integral light leads are less compatible, especially Olympus, as most urologists will not already have a Keymed light source, though adaptors are available (Pentax provides one free of charge). The use of a separate light lead seems most sensible (Wolf). Finally, cost may be considered an important determinant, but all instruments are several times the price of their rigid counterparts. Current prices (excluding VAT in the UK) are Wolf £4990, Storz £5495, Pentax £5500 (FCY 15H £7000) and ACMI and Olympus both £6500. Olympus purchasers might also need a Keymed light source (from £765) and a leak tester (£210) which also requires a suitable compressed air pump. The Pentax leak tester is £100.

Acknowledgements

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Extracorporeal Shockwave Lithotripsy or Extracorporeal Piezoelectric Lithotripsy? Comparison of Costs and Results

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Summary—One thousand patients with renal stones up to 3 cm in diameter were divided equally into 2 groups matched for age, sex and stone size. One group was treated on the Dornier HM3 lithotriptor and the other on the EDAP LT01. The results showed that for stones < 1 cm both lithotriptors were equally effective, with a stone-free rate of 87.5% for the Dornier and 90.4% for the EDAP at 3 months. The success rate fell more steeply for the EDAP machine, however, to become 77.2 and 42.5% respectively as the stone size increased to 3 cm. Treatment time was longer on the EDAP lithotriptor and more sessions were required but patients preferred it to the Dornier. Running costs per patient were higher on the EDAP.

Five years ago the first extracorporeal shockwave lithotripsy (ESWL) machine, a Dornier HM3 model, was installed by the state in Athens and our results with the first 2000 lithotripsies have been reported (Sofras *et al.*, 1988). In July 1987 an EDAP LT01 lithotriptor was installed in a private institution and the team of urologists already operating the Dornier were employed to operate the EDAP lithotriptor as well. By the beginning of July 1989 over 8000 patients had been treated on the Dornier and over 1500 on the EDAP lithotriptor. The 2 machines have different modes of stone localisation and shockwave generation (Coleman and Saunders, 1987) but in non-comparative reports similar end results and stone-free rates have been claimed (Palfrey *et al.*, 1986; Kiely *et al.*, 1989). We felt that a comparison of the results and costs would be of interest to anyone contemplating the purchase of a lithotriptor.

Patients and Methods

The Dornier group included 310 males and 190 females with a mean age of 47.2 years. The EDAP group comprised 276 males and 224 females with a mean age of 43.9 years. The first 300 patients treated on the EDAP lithotriptor were excluded as it was felt essential to treat at least this number of patients for the staff to become proficient in stone localisation. These patients were matched for stone size with a group treated by the Dornier lithotriptor and were divided into Group A (Dornier treated) and Group B (EDAP treated). They were further divided into 3 groups according to stone size (Fig. 1). In Group A, 116 patients had stones <1 cm in diameter, 250 had stones of 1 to 2 cm and 134 had

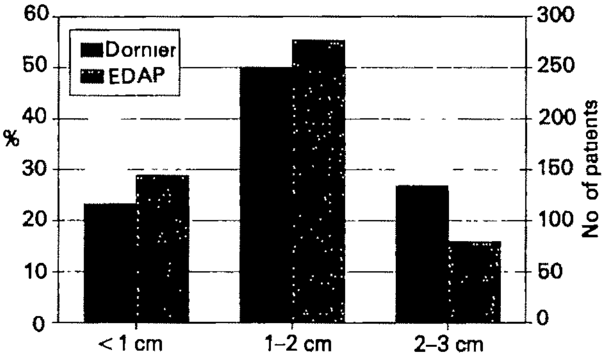

Fig. 1 Distribution of patients according to stone size.

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stones of 2 to 3 cm; in Group B the distribution was 144, 277 and 79 respectively. Stone size was measured on the plain abdominal X-ray as the largest diameter. Larger calculi were excluded from the study but stones of the upper ureter were included.

All patients were fully investigated, including clotting factors and ECG. All were hospitalised for 1 day for the first treatment. Follow-up was at 1 and 3 months. Second or third sessions were performed on an out-patient basis for the EDAP group and as in-patients for the Dornier group. The interval between re-treatment was 4 to 6 weeks.

Results

More sessions were required with the EDAP lithotriptor. Of the patients with stones <1 cm, 96.5% of the Dornier group had only 1 session and 3.5% 2 sessions. This compared with 66.6 and 23.6% of the EDAP group respectively; 9.7% of patients in the EDAP group with stones <1 cm had more than 2 sessions. Patients treated on the Dornier with stones 1–2 cm had 1 session in 92.8% of cases, 2 sessions in 5.6% of cases and 3 sessions in 1.6% of cases, compared with 40.4, 36.1 and 17.3% in the EDAP group. For stones 2–3 cm, 81.3% had 1 session, 14.9% 2 sessions and 3.7% 3 sessions in the Dornier group compared with 23.7, 28.9 and 73.6% respectively in the EDAP group.

The overall result at 3 months (Fig. 2) shows that the stone-free rate was 76.2% for the Dornier and 68.6% for the EDAP group. If the results are considered according to stone size, for stones of up to 1 cm 87.5% of the Dornier and 90.4% of the EDAP group were stone-free at 3 months (Fig. 3) compared with 80.2% and 70.4% for stones of 1 to 2 cm in each group respectively (Fig. 4). For larger stones the stone-free percentage fell to 77.2% for the Dornier and 42.5% for the EDAP group (Fig. 5). More sessions with the EDAP lithotriptor provided a good stone-free result but this was not comparable to the Dornier lithotriptor.

The overall clearance rate was better for renal stones compared with upper ureteric stones. There was an approximately 70% advantage for the Dornier in both groups.

There were virtually no complications in either group. Forty-two patients in Group A (8.4%) and 36 in Group B (7.1%) developed Steinstrasse; this difference was not statistically significant. All were managed conservatively with double pigtail stents inserted in 29 and 24 patients respectively.

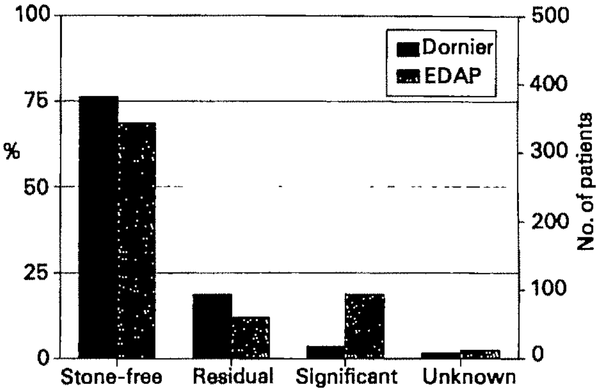

Fig. 2 Overall results at 3 months.

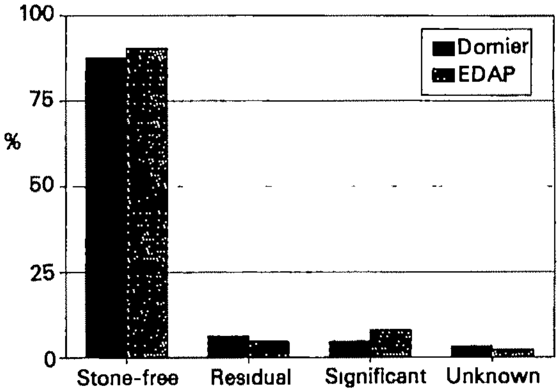

Fig. 3 Results for stones <1 cm.

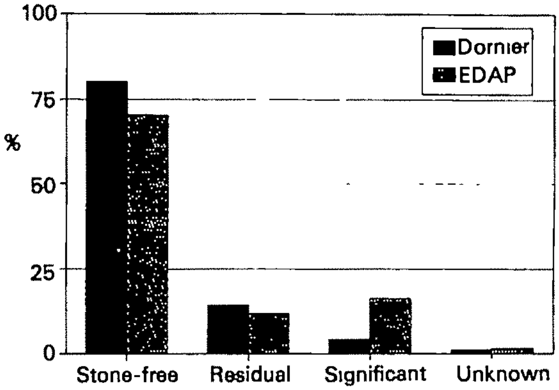

Fig. 4 Results for stones of 1 to 2 cm.

Running costs were difficult to assess because the Dornier lithotriptor was funded by the state and the EDAP on a private patient basis. We have based our calculation on the salaries of the medical and paramedical staff and the approximate cost of

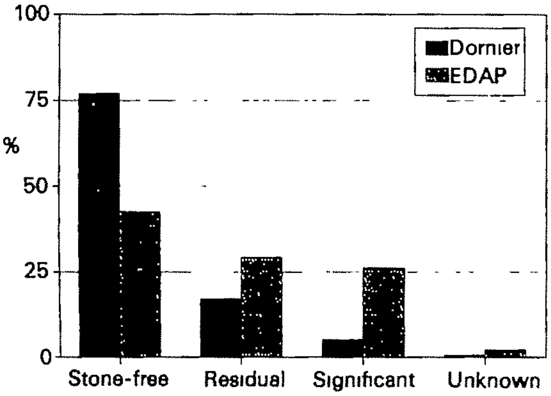

Fig. 5 Results for stones of 2 to 3 cm

disposable materials necessary to run the lithotriptors for 1 month for 100 patients. The cost (in sterling) was approximately £301 for Group A and £149 for Group B.

Discussion

Lithotripsy is now established as the treatment of choice in the management of renal calculi, with less than 10% of patients requiring an open procedure. The number of different lithotriptors and the high cost of purchase and maintenance underline the importance of making the correct decision as to which is the most suitable. Since the 2 methods employ different means of generating shockwaves, the energy administered is not comparable. It was felt that the total treatment time should not be a factor because the amount of energy delivered per shockwave also differs. It is, however, obvious that the EDAP lithotriptor requires more time to disintegrate a stone and we have limited the period of treatment per session to 1 h with this machine. All machines are safe for the patient and all appear to disintegrate the calculus. The high energy administered by the Dornier models reduces the time required to complete treatment. The damage to tissue is generally minimal, but on 2 occasions we have had to remove kidneys that were completely destroyed in patients subjected to repeated sessions within a short time on the Dornier lithotriptor (Sofras *et al.*, 1990). Repeat sessions are necessary for stones larger than 2 cm, but fewer are required with the Dornier machine. Radiolucent calculi requiring special techniques with the Dornier are well visualised on the EDAP, although the result of the procedure is less obvious. Upper ureteric stones are more difficult to clear than pelvic or caliceal stones, especially on the EDAP lithotriptor where stone localisation is extremely difficult, and in some cases the procedure had to be abandoned. The Dornier machine appears to fragment the stone into larger particles and the number of obstructions is higher, but not statistically so. The same applies to additional procedures performed on these patients but it should be noted that we use double pigtail stents on all patients with stones >2 cm.

Our results are similar to those presented by Rassweiler *et al.* (1987) and the small differences between the 2 studies are probably due to differences in the lithotriptors used.

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Anaesthesia-free Extracorporeal Shock Wave Lithotripsy in Patients with Renal Calculi

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Summary—Modern extracorporeal shock wave lithotripsy can be performed with combined ECG and respiratory triggered shock wave release. Disconnecting the ECG triggering increases the risk of ventricular arrhythmias, including potentially malignant ones. The aim of this study was to assess the relationship of any sympatho-adrenal excitation as a possible explanation for the occurrence of cardiac arrhythmia.

Plasma catecholamine levels were assessed in 5 patients during and after 50 min of anaesthesia-free extracorporeal shock wave lithotripsy for the treatment of calculi in the upper pole of the left kidney. Venous blood sampling showed no significant increase in catecholamines (epinephrine, norepinephrine and dopamine) during or after treatment. The heart rate and arterial blood pressure were measured simultaneously and showed no significant increase when shock waves were released during ECG triggering. However, when disconnecting the ECG-triggering mode, the incidence of ventricular extrasystoles on Holter monitoring became more apparent during respiratory triggered shock wave release only, although there was no rise in plasma catecholamine levels.

These data suggest that cardiac arrhythmias are related to direct and accidental mechanical stimulation of the heart rather than to any sympatho-adrenal discharge during shock wave release.

Since its introduction in the early eighties (Chaussy *et al.*, 1982), extracorporeal shock wave lithotripsy (ESWL) (Dornier Medical Systems, Marietta, USA) has become the treatment of choice in patients with urinary tract calculi. ESWL began in June 1987 with the Siemens Lithostar (Siemens Medical Engineering Group, Erlangen, Germany); 7500 procedures had been carried out by April 1990. These were performed without anaesthesia on an out-patient basis. The low invasiveness of the Lithostar is mainly related to the pressure amplitudes of the generated shock waves (Folberth, 1989). This allows treatment of larger stones as multiple staged procedures can be carried out with low morbidity. Successful monotherapy was achieved in larger stone volumes (Vandeursen and Baert, 1990a and b) and treatment of calculi throughout the urinary tract can be performed regardless of their location, since patients can be installed comfortably in both the prone and supine position.

It is felt that stone composition rather than size or location is more important in determining the success of ESWL treatment.

Earlier experience with the first generation extracorporeal shock wave lithotriptors reported an incidence of arrhythmia of 80% during the procedure, even when focusing perfectly on the stone (Chaussy and Schmiedt, 1983). Shock wave release 20 ms after the R-wave of the patient's electrocardiographic course (ECG triggered mode), as is possible with the modern lithotriptors, eliminates the risk of occurrence of extrasystoles if the shock waves should inadvertantly hit the cardiac region during the vulnerable T-phase (Ector *et al.*, 1989). Respiratory triggering is now also performed

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in the renal and upper ureteric locations; shock waves are released during expiration only, not only to target the stone perfectly but also to lower the risk of accidental firing on the lungs or heart.

We wished to study catecholamine plasma levels when shock waves were applied to the left upper pole of the kidney; the vicinity of this location near both heart and adrenal gland is ideal because the effect of the shock wave on both organs can induce arrhythmia. Assessing both the cardiac rhythm and the plasma catecholamine levels is relevant for the origin of arrhythmia occurring during ESWL. Either sympatho-adrenal stimulation or direct heart excitation by the shock wave itself can then be distinguished as a cause of the arrhythmia.

Patients and Methods

In 5 patients scheduled for ESWL, plasma catecholamine levels were assessed before, during and after treatment. The calculi were all located in the upper pole of the left kidney. The group comprised 4 males and 1 female, aged between 46 and 70 years (mean 49). None had a history of cardiovascular disorder or cardiac arrhythmia, except for mild arterial hypertension in 3 cases controlled by dietary restrictions. None of the patients had received medication specifically affecting the sympathetic nervous system.

All patients were treated with the Lithostar without anaesthesia. Only mild sedation with a benzodiazepine (1 mg lorazepam) was administered orally approximately 30 min before the start of treatment. ESWL was started in the combined ECG and respiratory triggered mode, but at certain moments the ECG triggering was discontinued. Shock wave electrical discharge ranged from 16 to 19 kV and the number of shock waves per kidney and per session ranged to 3000. Heart rate and arterial blood pressure were recorded at each blood sampling time. Holter monitoring (Oxford Medilog 4000-II recorder) was initiated 30 min before lithotripsy and was continued for 30 min after the procedure.

Venous blood sampling for plasma catecholamine assay by high performance liquid chromatography with electrochemical detection (Bauensfeld *et al.*, 1984) was carried out at the following times: baseline control values 10 and 5 min before and at the start of ESWL (T0, T5, T10), during the procedure after 10, 20, 30, 40 and 50 min of shock wave applications (T20, T30, T40, T50 and T60) and thereafter 5, 10, 15 and 20 min (T65, T70, T75 and T80) after stopping treatment. During the control baseline period all patients were positioned on the Lithostar table 10 min before sampling in order to avoid sympathetic stimulation by stress apart from a possible ESWL-related catecholamine release by stimulation of the adrenal medulla.

Results

Individual plasma catecholamine concentrations were recorded, including norepinephrine, epinephrine and dopamine (Tables 1, 2 and 3). The upper limits of normal reference values for the 3 catecholamines were: norepinephrine 300 ng/l, epinephrine 150 ng/l and dopamine 100 ng/l. The mean catecholamine profiles before, during and after ESWL are shown in Figure 1; no significant change in plasma levels of norepinephrine, epinephrine or dopamine was observed during or after the procedure in any of the 5 patients. Tables 4 and 5 reveal no significant changes in arterial blood pressure or heart rate (Figs 2 and 3). Holter monitoring revealed no cardiac arrhythmia with combined ECG and respiratory triggered shock wave release. When firing with only respiratory triggering, solitary ventricular extrasystoles occurred in 2 patients; all were symptomatic and transient.

Discussion

When compared with the baseline control values, no increase in the plasma concentrations of norepinephrine, epinephrine or dopamine was observed during or after lithotripsy. The mean baseline values of norepinephrine ranged between 370 and 470 ng/l before lithotripsy, which is slightly higher than the upper limit of the normal range: this may be related to the "non-basal" conditions due to emotional stress in the patients during the whole treatment period. However, it is interesting to note the absence of any increase during the procedure with repeated shock wave applications (Fig. 1). When carried out in the combined ECG and respiratory triggered mode, no increase in heart rate or blood pressure was found and no rhythmic disorder was noted in any patient.

The absence of any significant increase in plasma catecholamine levels together with the lack of cardiac arrhythmia or extrasystoles, or changes in arterial pressure during combined respiratory and ECG triggered shock wave release, indicates that the influence of ESWL on cardiac activity reported by Chaussy and Schmiedt (1983) and Ector *et al.* (1989) may be related to direct cardiac excitation

Table 1 Individual Plasma Norepinephrine Levels (ng/l)

	Patient 1 (male, 62 years)	*Patient (male, 61 years)*	*Patient 3 (female, 47 years)*	*Patient 4 (male, 57 years)*	*Patient 5 (male, 77 years)*	*Average*	*SD*
T0	470	404	246	361	417	379.6	±84 2
T5	489	361	290	490	462	418	±89.1
T10	578	512	301	440	492	464	±103.9
T20	510	362	251	595	497	443	±135 9
T30	542	391	266	476	519	438.8	±112.4
T40	505	406	190	370	515	397.2	±131.5
T50	466	508	127	390	492	396 6	±157.3
T60	579	569	129	299	443	403.8	±191
T65	516	482	137	370	441	389.2	±151 1
T70	415	530	195	448	420	401 6	±124.3
T75	450	514	196	350	413	384.6	±121
T80	418	488	178	433	396	379.2	±137

Table 2 Individual Plasma Epinephrine Levels (ng/l)

	Patient 1 (male, 62 years)	*Patient 2 (male, 61 years)*	*Patient 3 (female, 47 years)*	*Patient 4 (male, 57 years)*	*Patient 5 (male, 77 years)*	*Average*	*SD*
T0	62	47	26	101	128	72.8	±41.2
T5	80	<25	22	22	128	55.4	±47.5
T10	176	48	18	44	131	83 4	±66 9
T20	70	24	<25	19	107	49.2	±38.4
T30	94	35	<25	26	93	54 6	±35 7
T40	53	25	40	17	118	50 6	±40.1
T50	112	<25	15	25	115	58 4	±50
T60	97	<25	24	70	133	69.8	±47.0
T65	41	<25	14	34	125	47.8	±44 3
T70	46	<25	19	51	131	54 4	±44.9
T75	49	41	20	26	142	55.6	±49 6
T80	63	25	<25	26	123	52.4	±42 7

Table 3 Individual Plasma Dopamine Levels (ng/l)

	Patient 1 (male, 62 years)	*Patient 2 (male, 61 years)*	*Patient 3 (female, 47 years)*	*Patient 4 (male, 57 years)*	*Patient 5 (male, 77 years)*	*Average*	*SD*
T0	<25	61	<25	<25	<25	32.2	±16.0
T5	71	64	<25	25	<25	42	±23.4
T10	55	59	<25	25	<25	37.8	±17.5
T20	25	<25	<25	25	<25	25	±0
T30	54	38	<25	25	<25	36	±11 9
T40	53	<25	<25	25	<25	30.6	±12.5
T50	70	51	<25	25	<25	39.2	±20.5
T60	100	49	<25	25	<25	44 8	±32.5
T65	52	53	<25	25	<25	36	±15.0
T70	59	55	<25	25	<25	37.8	±17.5
T75	<25	<25	<25	51	95	44.2	±30 5
T80	46	66	<25	25	<25	37.4	±18.3

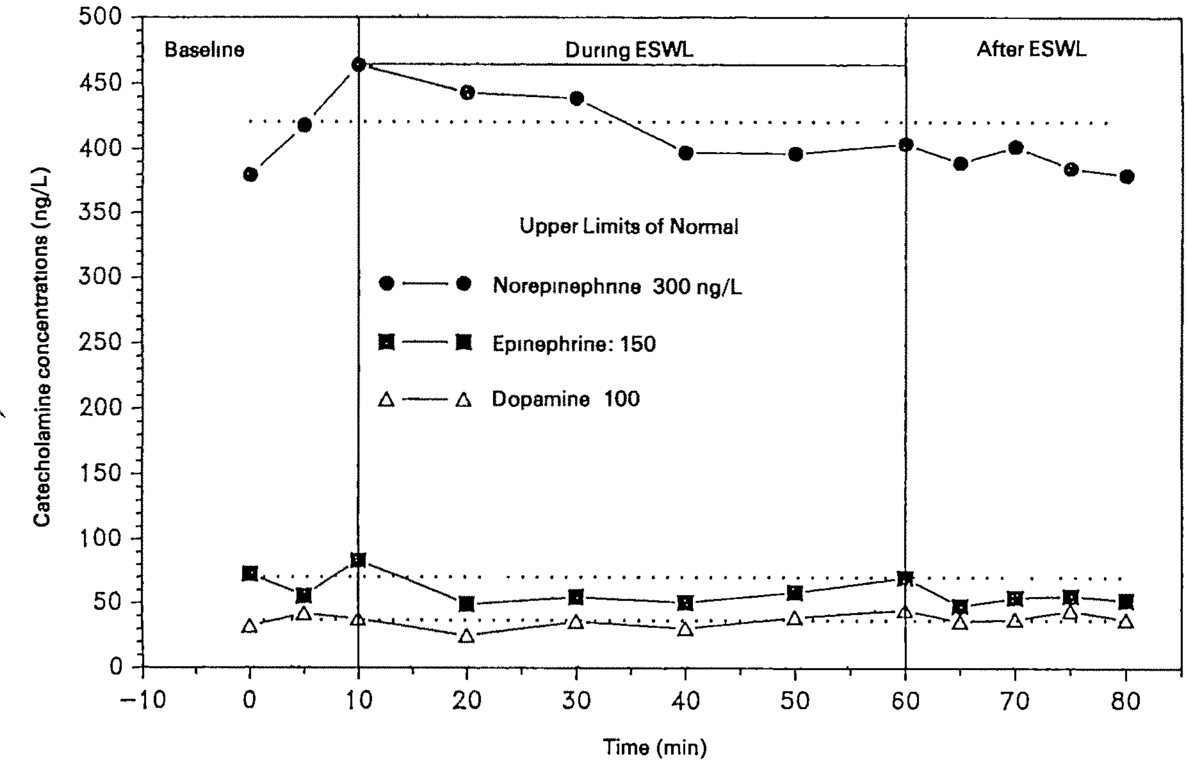

Fig. 1 Mean catecholamine profiles of 5 patients during anaesthesia-free ESWL

by the shock waves rather than due to catecholamines from sympatho-adrenal stimulation. We found that when omitting the ECG triggering, Holter monitoring showed solitary ventricular extrasystoles. Although transient and asymptomatic, the significance of this observation lies in the rhythm disorder occurring without biochemical evidence of sympatho-adrenal excitation. Even though modern lithotriptors have a well delineated focal area of shock wave interaction on the target, the present data make the importance of ECG triggered ESWL more convincing. Respiratory triggering is mandatory for precise focusing on the calculus (during shock wave release), especially when located in a part of the urinary tract subject to the respiratory movement of the kidney. The combination with ECG triggering discloses a supplementary safety control by releasing the shock wave on the targeted region, withdrawing accidental cardiac stimulation in the vulnerable phase of cardiac pacing. Since the treatment is anaesthesia-free, the problem of spontaneous movement by the patient remains a possible reason for inadvertent shock wave release beneath the target, although the release was initially perfectly adjusted. This also emphasises the need for regular focus controls during the procedure by fluoroscopy and/or sonography rather than a blind shock wave delivery.

Technological improvements in extracorporeal shock wave lithotriptors allow a precise focus to be seen on which to target the shock waves. The modern devices also permit respiratory triggering, making inadvertent firing beneath the stone due to mobility by respiration unlikely. Clinical experience, however, has shown the possibility of cardiac arrhythmia occurring during shock wave release. Although modern lithotriptors now have a well delineated focal region of shock wave interaction on the target and an exact stone detection method, accidental firing beneath the target due to movement by the patient still cannot be excluded. This remains possible as most treatments are performed anaesthesia-free. The present findings in relation to plasma catecholamine responses (norepinephrine, epinephrine and dopamine) from 5 patients before, during and after an ESWL-procedure lasting for 50 min demonstrate the lack of biochemical evidence for excessive norepinephrine/epinephrine release from an inadvertent sympatho-adrenal discharge by the ESWL procedure. These

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Table 4 Individual Arterial Blood Pressure Values (Psyst/Pdiast/Pmean mmHg)

		Patient 1 (male, 62 years)	*Patient 2 (male, 61 years)*	*Patient 3 (female, 47 years)*	*Patient 4 (male, 57 years)*	*Patient 5 (male, 77 years)*	*Average*	*SD*
T0	Psyst	170	180	120	140	140	152.5	27.5
	Pdiast	90	70	80	105	95	88	13.5
	Pmean	130	125	100	122.5	117.5	119	11.5
T5	Psyst	190	180	120	135	135	152	30.9
	Pdiast	100	70	80	105	90	89	14.3
	Pmean	145	125	100	120	112.5	120.5	16.6
T10	Psyst	195	195	120	140	140	158	34.7
	Pdiast	110	65	80	100	100	92	18.9
	Pmean	152.5	130	100	120	120.5	124.6	19
T20	Psyst	180	160	115	140	150	149	24
	Pdiast	100	65	85	105	110	93	18.2
	Pmean	140	112.5	100	122.5	130	121	15.4
T30	Psyst	170	180	120	135	130	147	26.3
	Pdiast	90	65	90	100	95	88	13.5
	Pmean	130	122.5	105	117.5	112.5	117.5	9.5
T40	Psyst	180	170	125	135	120	146	27.2
	Pdiast	105	70	90	100	95	92	13.5
	Pmean	142.5	120	107.5	117.5	107.5	119	14.3
T50	Psyst	185	190	135	135	130	155	29.8
	Pdiast	90	65	95	100	100	90	14.6
	Pmean	137.5	127.5	115	117.5	115	122.5	9.8
T60	Psyst	190	200	130	135	130	157	34.9
	Pdiast	100	75	85	100	110	90	12.2
	Pmean	145	137.5	107.5	117.5	120	125.5	15.3
T65	Psyst	175	185	120	140	140	152	27
	Pdiast	105	75	90	105	95	94	12.4
	Pmean	140	130	105	122.5	117.5	123	13.1
T70	Psyst	160	170	130	140	130	146	18.1
	Pdiast	95	70	90	100	95	90	11.7
	Pmean	127.5	120	110	120	112.5	118	6.9
T75	Psyst	165	170	125	140	130	146	20.4
	Pdiast	100	65	85	105	95	90	15.8
	Pmean	132.5	117.5	105	122.5	112.5	118	10.3
T80	Psyst	160	175	120	140	135	146	21.6
	Pdiast	95	70	90	110	100	93	14.8
	Pmean	127.5	122.5	105	125	117.5	119.5	8.9

Pmean = Arithmetic mean arterial blood pressure.

Table 5 Individual Heart Rates (beats/min)

	Patient 1 (male, 62 years)	*Patient 2 (male, 61 years)*	*Patient 3 (female, 47 years)*	*Patient 4 (male, 57 years)*	*Patient 5 (male, 77 years)*	*Average*	*SD*
T0	87	57	78	83	76	76.2	11.5
T5	85	57	78	85	75	76	11.5
T10	82	58	73	75	95	76.6	13.5
T20	72	60	79	77	89	75.4	10.6
T30	81	59	75	78	94	77.4	12.6
T40	78	54	81	78	78	73.8	11.1
T50	70	58	79	73	82	71.8	9.4
T60	68	56	79	70	82	71	10.2
T65	65	56	80	75	72	69.6	9.3
T70	63	55	73	75	75	68.2	8.9
T75	72	55	75	78	72	70.4	8.9
T80	67	56	78	72	77	70	8.9

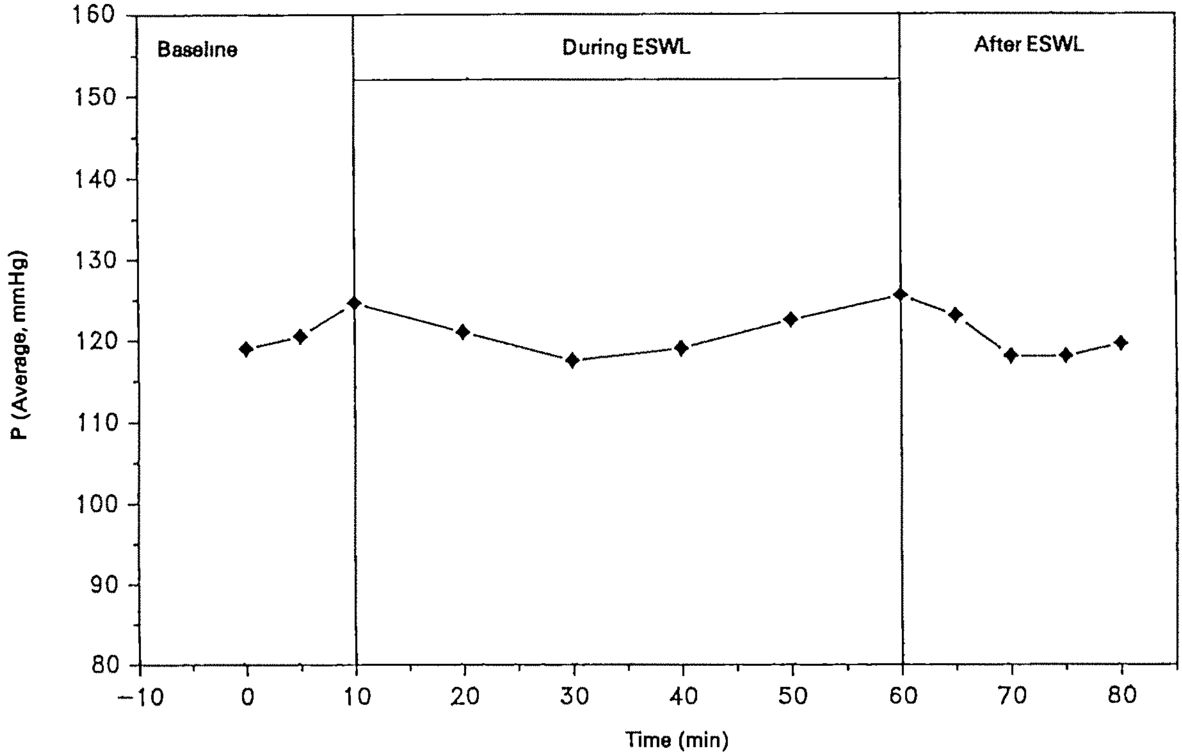

Fig. 2 Arithmetic mean arterial blood pressure in 5 patients during anaesthesia-free ESWL.

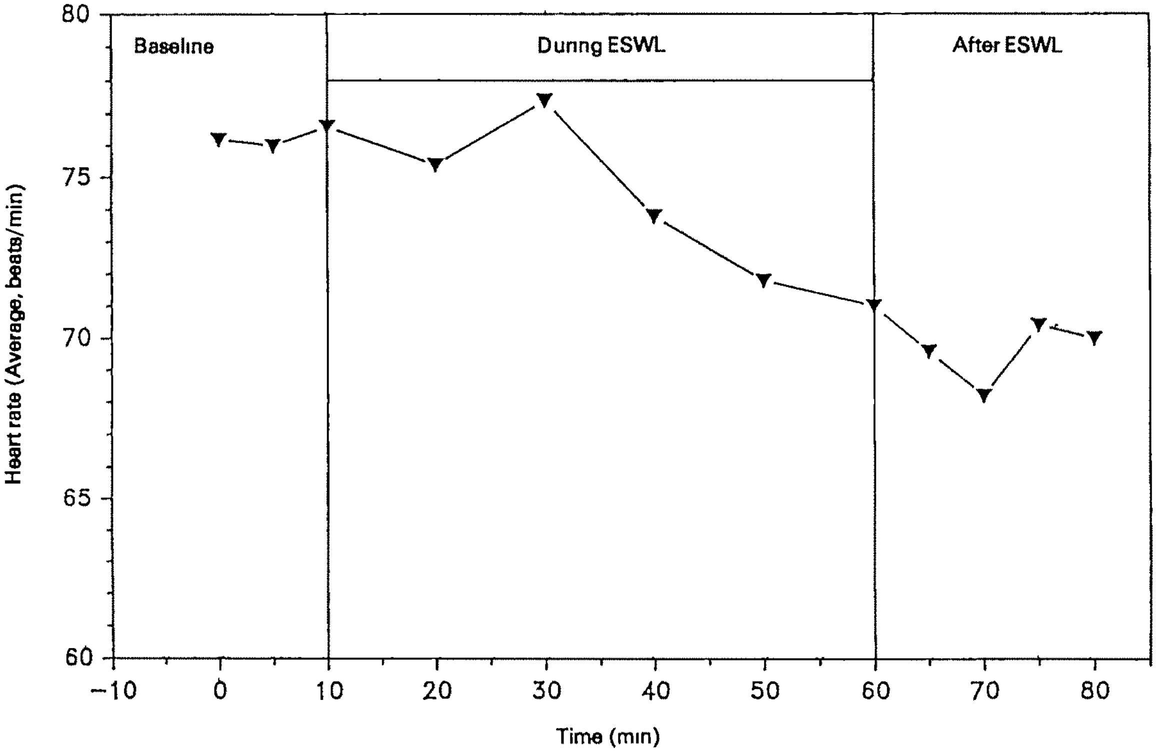

Fig. 3 Mean heart rate in 5 patients during anaesthesia-free ESWL

findings also indicate that the occasionally arrhythmia observed during ESWL (Ector *et al.*, 1989) is unlikely to be related to an excessive catecholamine release during the procedure and is more likely to be associated with direct mechanical stimulation of the heart.

Thus the possibility of combined ECG triggering makes the procedure safer by lowering the risk of shock wave-induced cardiac excitation, especially when treating calculi in the upper pole of the left kidney.

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Do not Catheterise your Nephrectomies

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Summary—A retrospective study of 100 consecutive nephrectomy patients showed a 20% catheterisation rate. Of the 11 carried out post-operatively only 4 were for urinary retention. The post-operative catheterisation rate for males was 7.1% and for females 2%. The rate of post-operative retention was 4.4%, which is much lower than that reported from other units. This rate of post-operative catheterisation for retention is so low that in spite of the very mild increase in complications compared with intra-operative catheterisation, the practice of routine prophylactic catheterisation of nephrectomy patients is unnecessary and cannot be recommended.

Recent reports have recommended the routine intra-operative catheterisation of patients aged over 40 who are undergoing nephrectomy (Davies *et al.*, 1989; Cetti, 1990). This recommendation stems from their excessively high rate of post-operative retention and the apparent advantage of carrying out catheterisation in the operating theatre. This has not been our experience, and we therefore undertook a review of the catheterisation rate amongst nephrectomy patients in our District General Hospital urological service.

Patients and Methods

The complete case records of 100 consecutive patients who had undergone planned nephrectomy were identified from the Medical Records Department coding system. All personal details of the patients were recorded together with the operative approach and pathology. Patients undergoing a nephroureterectomy were excluded, as were the 6 patients who had had a nephrectomy incidental to another procedure. Evidence for catheterisation was sought from 4 different places within each set of case notes. The medical, anaesthetic and nursing notes were examined and the fluid balance charts were checked. In this way all patients requiring catheterisation were detected. Five sets of notes that were clearly incomplete were excluded.

Results

The 100 nephrectomies were carried out over a 6-year period and involved 46 males and 54 females ranging in age from 20 months to 90 years (mean 53 years); 74 patients were 40 years old or more and 16 men (44%) and 32 women (59%) were aged over 60 years. Carcinoma accounted for 43 patients, 48 patients had 'end-stage' kidney due to infection, stones, hydronephrosis or pelviureteric obstruction. The 9 remaining patients had various pathologies.

Twenty of 100 patients were catheterised, 3 pre-operatively and 6 intra-operatively. Only 11 of the remaining 91 patients required post-operative catheterisation and the majority of these (7: 64%) were for low urinary output; only 4 were for retention of urine, of whom 3 were male. The male post-operative catheterisation rate for retention of urine was 7.1% (3 of 42 remaining males) and the female rate 2% (1 of 49 remaining females). The majority of patients catheterised (85%) were more than 60 years old. The 3 pre-operative catheterisations were for clot retention and the 6 intra-operative catheterisations were for per-operative hypotension (4) or losing the ureteric tie (2).

Of the 6 catheterised patients who developed significant bacteriuria (colony count $>10^5$/ml), 4 had been catheterised post-operatively. The complication rate from post-catheterisation bacteriuria was negligible. One patient developed epididymo-orchitis after intra-operative catheterisation. The pathology of the kidney did not affect the catheter-

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isation rate, nor did the surgical approach. Two of the 3 males who went into urinary retention required a prostatectomy.

Discussion

Catheterisation is an invasive procedure with possible complications (infection, stricture, *etc*) and should therefore be avoided. Our rates for catheterisation are lower than those reported by Davies *et al.* (1989) and the 23% rate reported for laparotomy by Stallard and Prescott (1988), and equal to the earlier authors' quoted rate for cholecystectomy. Although in our hands catheterisation did cause some cases of significant bacteriuria, the number of patients who went on to develop a complication, or whose convalescence was delayed, was not significant.

Retention of urine following nephrectomy is very uncommon in our unit (4.4%) and does not justify routine prophylactic peri-operative catheterisation of all nephrectomy patients. We recommend that the usual expectant policy, as with other abdominal surgery, is followed. Catheterisation is warranted only in those patients who have specific pre- or intra-operative requirements or who develop retention.

Acknowledgement

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The Effect of Cromakalim on the Normal and Hyper-reflexic Human Detrusor Muscle

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Summary—Cromakalim is a benzopyran derivative which relaxes smooth muscle, probably by opening membrane potassium channels.

This study tested the effect of cromakalim on spontaneous, electrically induced and pharmacologically induced contractile activity of normal and hyper-reflexic human detrusor muscle samples. All 3 types of contractile activity were reduced in the presence of cromakalim.

A preliminary clinical trial of cromakalim was conducted, the results of which also suggest that this type of drug may have a significant role in the treatment of detrusor instability and hyper-reflexia.

Our understanding of the physiology of the lower urinary tract both in health and disease remains incomplete. Not surprisingly, therefore, our treatment of bladder dysfunction, particularly detrusor instability and hyper-reflexia, is far from ideal. At present anticholinergic agents, such as oxybutynin, remain the drugs of choice but these are plagued by side effects and at doses required for relief of symptoms side effects such as dry mouth seem to be the rule. Although some patients with severe symptoms will accept these side effects, many patients find them intolerable.

Drugs with alternative modes of action that might have more beneficial effects with fewer side effects have been sought. Terodiline is one such agent which is thought to act as a calcium channel blocker with some anticholinergic properties. Results have been variable and require further controlled studies.

Speakman *et al.* (1988), on the basis of their experimental studies, have suggested membrane stabilisers as an alternative or supplement to neuromuscular blockade with anticholinergic agents. One possible drug of this type is cromakalim, (+)-*trans*-6-cyano-3,4-dihydro-2,2-dimethyl-4-(2-oxo-1-pyrrolidyl)-2H-1-benzopyran-3-ol, which is a member of a novel group of benzopyran derivatives. It has been shown to have potent antihypertensive activity in conscious animals (Buckingham *et al.*, 1986) and has subsequently been found to have several other potential uses. It has a relaxant effect on a variety of smooth muscles, including vascular smooth muscle (Hamilton *et al.*, 1986), taenia caeci (Weir and Weston, 1986), trachealis (Allen *et al.*, 1986) and uterus (Hollingsworth *et al.*, 1987). This smooth muscle relaxation is probably due to the opening of potassium channels by cromakalim in muscle membranes promoting the outward conductance of potassium ions and hyperpolarisation of the cell membrane potential (Allen *et al.*, 1986; Hamilton *et al.*, 1986).

As yet only 2 *in vitro* studies have been reported on urinary bladder smooth muscle (Fujii, 1987; Foster and Brading, 1987, unpublished observations), both of which were carried out using tissue from experimental animals, guinea pig and pig respectively. The present study investigated the action of cromakalim on the human urinary bladder smooth muscle *in vitro*.

Materials and Methods

Detrusor muscle was obtained at surgery from 10 patients with urodynamically normal bladders and

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from 10 patients with urodynamically proven detrusor hyper-reflexia. Samples were immediately placed in ice-cold Krebs solution (composition mM: NaCl 118, KCl 4.7, $MgSO_4$ $7H_2O$ 1.18, $NaHCO_3$ 25, KH PO 1.03, CaCl 2.5, glucose 11.1) and stored at 4°C for 1 to 25 h. Muscle strips measuring 1 × 5 mm were set up in 1-ml organ baths containing Krebs solution kept at a constant 37°C and aerated with 95% O_2 and 5% CO_2 (Kinder and Mundy, 1987); 1 g of tension was applied and the strips (36 normal and 34 hyper-reflexic) were allowed to equilibrate for 90 min before any test was performed. In those strips which demonstrated spontaneous contractile activity (16/36 normal detrusor strips and 26/34 hyper-reflexic detrusor strips), the action of cromakalim at varying concentrations (10^{-9M}–10^{-5M}) was investigated.

The effect of the drug on the contractile response of the detrusor to electrical field stimulation was investigated in 13 normal and 12 hyper-reflexic detrusor strips. Frequency response curves were constructed (60 V, 0.5 ms pulse width, 0.5 ms duration for 5 s at 4-min intervals) for 0.5 to 30 Hz and repeated in the presence of cromakalim and then again after washout, to assess the reversibility of the drug's effect.

Dose response curves were obtained using acetylcholine as the contractile agent, in the presence and absence of cromakalim using 17 normal strips and 17 hyper-reflexic strips.

Results

Cromakalim 10^{-9M} failed to affect spontaneous contractions in all normal bladder samples, but in 1 hyper-reflexic bladder strip an 80% reduction in spontaneous activity was observed. Higher concentrations of cromakalim produced a dose-dependent inhibition of spontaneous activity in all bladder samples and doses of 10^{-7M} and above produced a total inhibition of spontaneous activity (Fig. 1). The effect of cromakalim began 2 to 4 min after its addition to the bath.

Cromakalim 10^{-9} to 10^{-8M} had no effect on the response to electrical stimulation in either the normal or the hyper-reflexic specimens. At concentrations of 10^{-7} to 10^{-5M} there was a concentration-dependent inhibition of contraction, which in some samples was 100%. This effect was reversible as the contractile response to electrical stimulation was restored to the same magnitude after washout of cromakalim (Fig. 2). There appeared to be no difference in the effect of cromakalim on the normal and hyper-reflexic detrusor strip response to electrical stimulation (Fig. 3).

When acetylcholine was the stimulating agent, cromakalim 10^{-9M} again produced no inhibitory effect. There was a slight inhibition of the acetylcholine contractile response in the presence of cromakalim at a concentration of 10^{-8M}, and concentrations of 10^{-7} to 10^{-5M} produced a marked

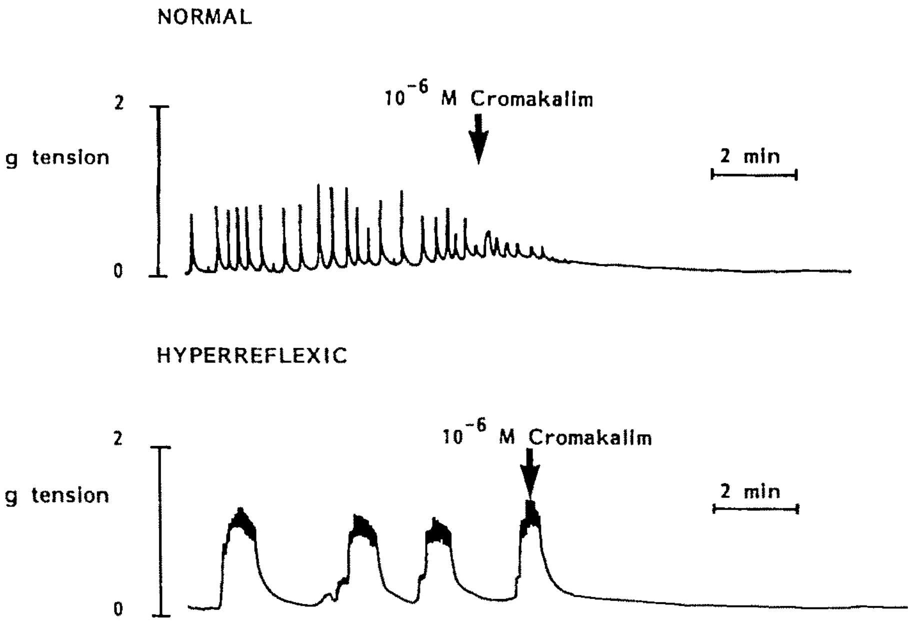

Fig. 1 Effect of cromakalim on spontaneous contractile activity of human detrusor

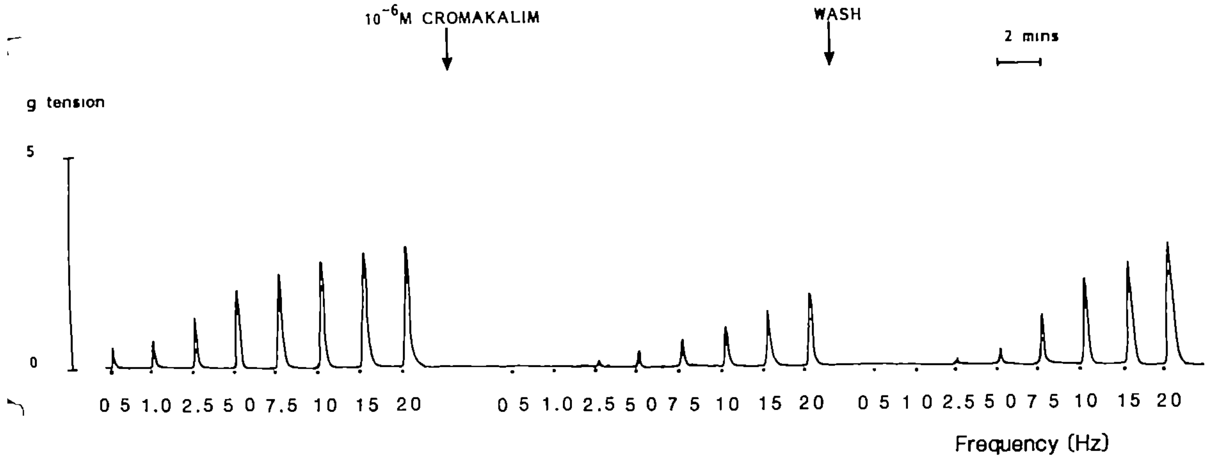

Fig. 2 Effect of cromakalim on response to electrical stimulation of human detrusor

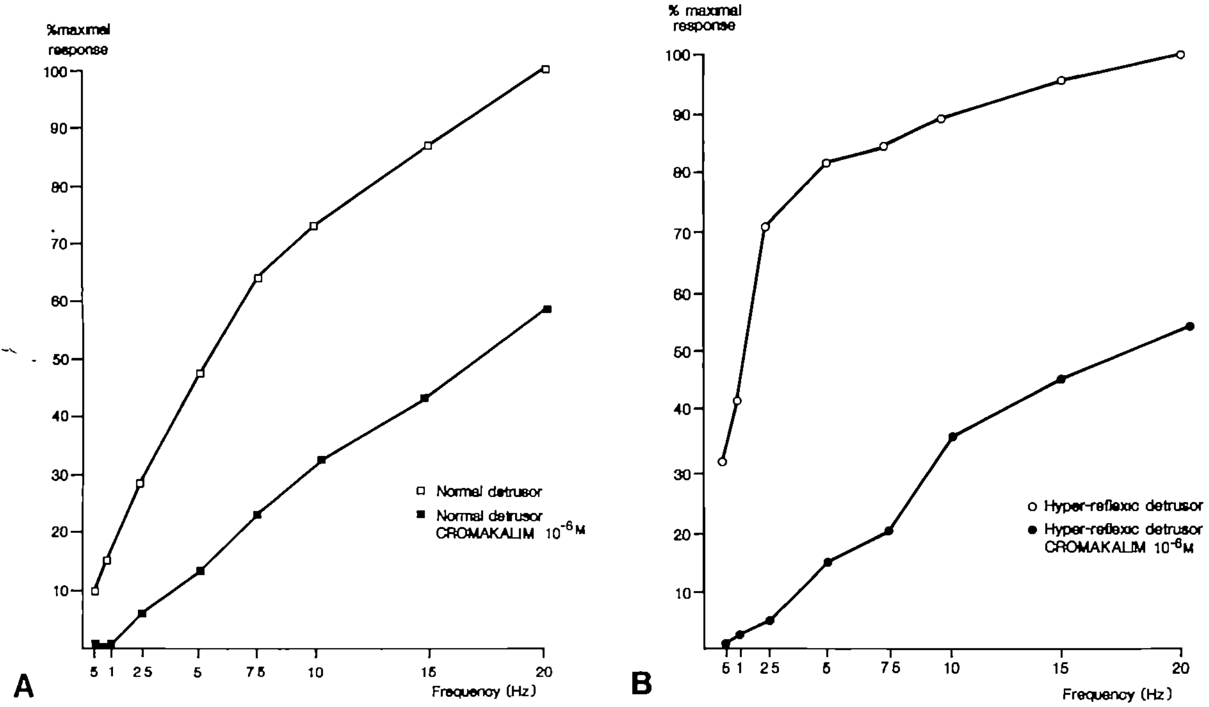

Fig. 3 (A) Normal bladder. Frequency response curve in the presence and absence of cromakalim (B) Hyper-reflexic bladder. Frequency response curve in the presence and absence of cromakalim.

inhibition of response to acetylcholine (Fig. 4). However, this inhibitory effect of cromakalim was less marked than it was against electrical stimulation.

Discussion

Cromakalim has been shown to produce a concentration-dependent hyperpolarisation of smooth muscle cell membranes, increased membrane potassium conductance and reduced amplitude of smooth muscle contractions in other studies (Hamilton *et al.*, 1986). The work of Foster and Brading (1987, unpublished observations) seemed to indicate species differences in the response of urinary bladder muscle to cromakalim. In guinea pig bladder cromakalim (10^{-6}–10^{-5}M) had no effect on carbachol-evoked and potassium-evoked contrac-

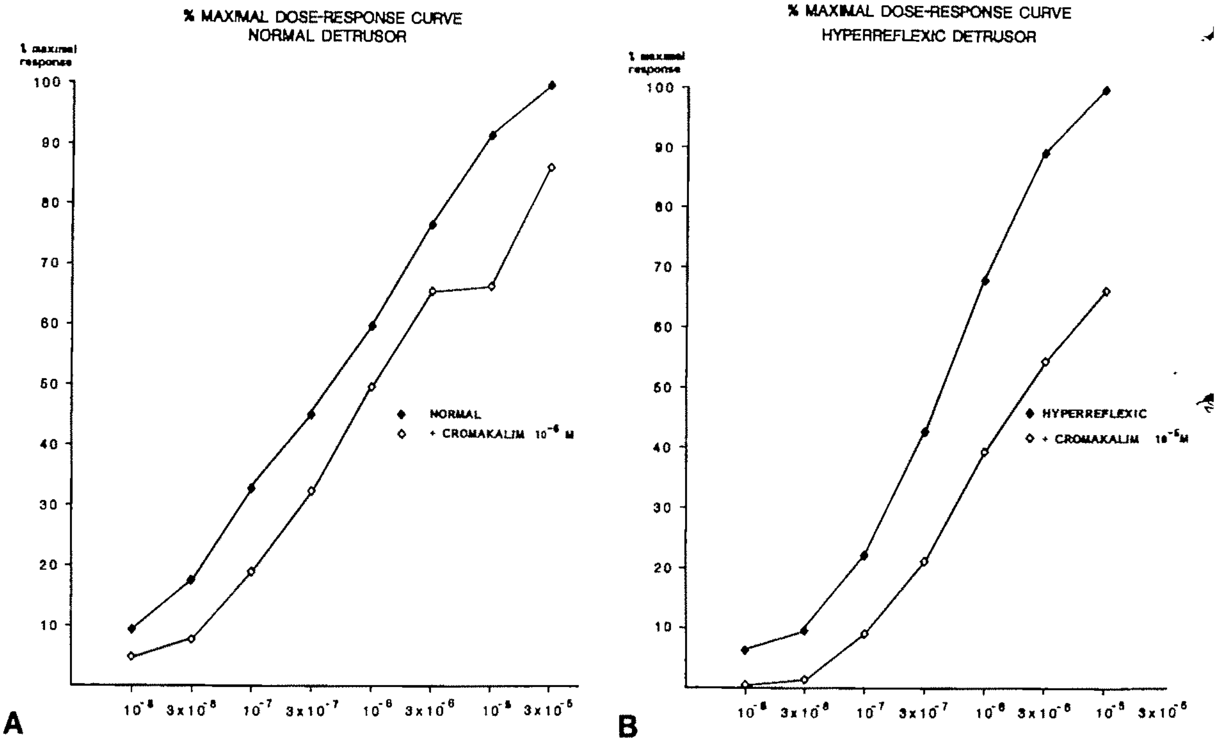

Fig. 4 (A) Normal bladder Dose response curve for acetylcholine in the presence and absence of cromakalim. (B) Hyper-reflexic bladder. Dose response curve for acetylcholine in the presence and absence of cromakalim.

tions or on the response to intrinsic nerve stimulation, whereas in the pig bladder there was a marked inhibition of response to carbachol and a slight but significant inhibition of potassium-evoked contraction at concentrations of 8×10^{-6M} to 10^{-5M} cromakalim. The present study, using human bladder samples, recorded a significant inhibition by cromakalim of contraction produced by intrinsic nerve stimulation and a dose-dependent, but less marked, inhibition of acetylcholine-evoked contractions.

Kinder and Mundy (1987) reported a series of studies on the pathophysiology of idiopathic detrusor instability and detrusor hyper-reflexia in humans and showed that a fundamental characteristic of detrusor muscle in these disease states is an increased incidence of spontaneous activity (which is itself of increased frequency and amplitude) when compared to normal detrusor in an *in vitro* organ bath preparation and a higher sensitivity to electrical stimulation of low frequency. The predominant effect of cromakalim on these 2 types of activity indicates that the drug might be useful clinically either alone—because anticholinergic drugs have no effect at all on spontaneous activity but only on induced activity, whereas cromakalim is effective on both—or in combination with an anticholinergic agent.

Brading (unpublished data) completed a preliminary *in vivo* study with cromakalim on pigs with detrusor instability and obtained promising results. We have carried out a pilot single-blind study of 17 patients with detrusor instability or detrusor hyperreflexia who had failed to achieve a satisfactory response with other drugs or who had ceased medication due to intolerable side effects, and the results were equally encouraging. Of the 17 patients, 16 completed the study; 6 patients (35%) responded to cromakalim with an improvement in symptoms of urinary frequency and with an objective increase in mean voided volume. One of these withdrew after 6 weeks because of side effects, 1 was lost to follow-up and 4 continued treatment after the initial trial period (3 with idiopathic detrusor instability and 1 with detrusor hyper-reflexia secondary to multiple sclerosis). Side effects were minimal, mainly headache, constipation and skin rash.

Unfortunately, soon after the preliminary clinical trial was completed, the drug was withdrawn because of the adverse effects of high doses in long-term toxicological studies in animals. Despite this, we feel that the results of the animal work of Foster and Brading (unpublished observations), together with the findings of the experimental human study and the preliminary clinical trial described here, suggest that there may be a role for this type of drug in the treatment of the unstable and hyper-reflexic bladder when a safer alternative to cromakalim has been developed.

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Long-term Effect of Pelvic Floor Exercises on Female Urinary Incontinence

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Summary—In order to assess the permanent effect of pelvic floor exercises on female stress incontinence, 76 incontinent women, referred for incontinence surgery, underwent a 3-month exercise programme conducted by an experienced physiotherapist.

The patients were followed up for 1 year. At the last assessment 30% were cured and 17% improved. Altogether 47% avoided surgery.

No relapses were seen during the follow-up period. Patients with mild incontinence benefited from intensified training, since 72% could expect to be cured, while patients with severe incontinence and no immediate effect did not benefit from further exercises. Patients with a positive hormone status and those with normal weight had a significantly higher cure rate.

The subjective results were confirmed by the 24-h pad test. Anal pressure profilometry was a valid method for instruction and objective control of pelvic floor function. It was concluded that pelvic floor exercises should precede surgery, since exercises had a permanent effect in half of the patients.

Several studies (Kegel, 1951; Kujansuu, 1983; Wilson *et al.*, 1987; Henella *et al.*, 1988) have confirmed the effect of pelvic floor exercises on female urinary incontinence, and since no side effects have been observed, this conservative approach is recommended before surgery is considered.

The results of the exercises have usually been evaluated shortly after the exercise programme and only a few reports (Klarskov *et al.*, 1989) have considered the long-term results. If the effect of the exercises is to be permanent, continuous awareness and activity of the pelvic floor are required, together with the adoption of new ways of heavy lifting, coughing, *etc*, in order to prevent overdistension of the pelvic floor. One might expect the patient's motivation for continuous exercises to decrease when she has become continent and is on her own at home. Wilson *et al.* (1987) reported better results from exercises conducted by an experienced physiotherapist in hospital compared with a home programme. If incontinence recurs after the exercise programme, it means that the exercises have delayed surgery rather than avoided it.

In this study we examine the results of a 3-month pelvic floor exercise programme, the duration of follow-up being 1 year. The results were evaluated subjectively by means of a 24-h pad test and by anal pressure profilometry. To define the patients who would benefit most from the exercise programme, the influence of several variables, *e.g.* body weight, type and degree of incontinence, hormone treatment, *etc*, was analysed.

Patients and Methods

A total of 100 patients, referred to the Departments of Obstetrics and Gynaecology or Urology for surgical treatment of their stress incontinence, were offered a 3-month pelvic floor exercise programme.

Excluded from the study were 3 patients with genital prolapse that required surgery and 10

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patients who attended less than half of the therapy sessions. Nine patients could not participate in the programme because of working commitments and 2 were lost to follow-up. This left 76 patients for final evaluation. The study was approved by the Ethical Committee.

Before entering the programme the following "patient variables" were recorded: age, parity, previous operations for incontinence or prolapse, and hormonal status (considered positive if the patient was pre-menopausal or receiving oestrogens). When classified according to body weight and height the patients were described as: normal/underweight or overweight (>10% normal weight) (Natvig, 1956). During pelvic examination the presence of a moderate or severe cystocele or rectocele was noted. Residual urine was measured by catheterisation and fast-fill CO_2 cystometry was performed in the supine position to detect overactive detrusor function as defined by the International Continence Society (Abrams *et al.*, 1988). Colpocysto-urethrography (CCU) was performed and the type of bladder descent was recorded as normal, anterior, posterior or combined (Olesen, 1982).

The following "result-variables" were recorded before the exercises and at each follow-up assessment. The grades of incontinence as defined by Ingelmann-Sundberg (1953) were: Grade I: incontinence only at coughing, heavy lifting, *etc*; Grade II: incontinence during daily activities such as raising from a chair, walking, *etc*; Grade III: dripping incontinence in the upright position. Complaints of frequency (>6 voidings/day), nocturia (>1 voiding/night), urge incontinence and urine leakage during a 24-h home pad test were also recorded.

The control and strength of the pubococcygeus muscle was measured by anal pressure profilometry (APP), as described by Kielmann and Bonnesen (1985). Three profiles at rest and 2 at withholding were recorded at each assessment. The average of the maximum pressure at rest and at withholding was calculated.

The 3-month exercise programme, which was conducted by an experienced physiotherapist, consisted of weekly group sessions in the hospital, each lasting 45 min. It included individual instruction in pelvic floor exercises, vaginal self-palpation to control the effect, exercises in different body positions, lessons in pelvic floor anatomy, lifting technique, advice concerning bladder and bowel emptying, and a home exercise programme for daily use during and after the hospital programme.

The results of the exercises were assessed subjectively as cured, improved or unchanged and according to the "result variables". The assessments took place immediately after the end of the programme and then 3 and 12 months later. At each appointment the patient could be referred for surgery, if the exercises had failed.

Statistical methods used were the X^2 test, analyses of variance and variance components analyses. The chosen level of significance was $P<0.05$ (unless otherwise indicated). Numbers in brackets after average values are 95% confidence limits.

Results

The median age of the 76 patients was 52 years (27–78) and mean parity was 2.0 (0–5); 3 patients were nulliparous. The distribution of "patient variables" and "result variables" before starting the exercise programme are listed in Table 1.

Table 1 Variables Recorded Before the Start of Pelvic Floor Exercises

Patient variables		*No of patients*	*% of total*
>10% overweight		24	31
Previous operations		7	9
Positive hormone status		50	66
Cystocele/rectocele		25	34
Residual urine >50 ml		22	40
Overactive detrusor		4	6
CCU-diagnosis normal		4	5
Posterior descent		23	30
Anterior descent		34	45
Combined descent		15	20
Result variables			
Grade of incontinence	I	25	33
	II	38	50
	III	13	17
Pure stress incontinence		56	74
Mixed stress-urge incontinence		20	26
Frequency		22	29
Nocturia		15	20

The subjective results at the 3 assessments, grouped according to pre-exercise stress grade, are presented in Figure 1. The patients referred for operation are listed as unchanged.

When relating stress grade to subjective outcome, no statistically significant difference in cure rate was seen between the stress groups at the first assessment, but at the subsequent examinations

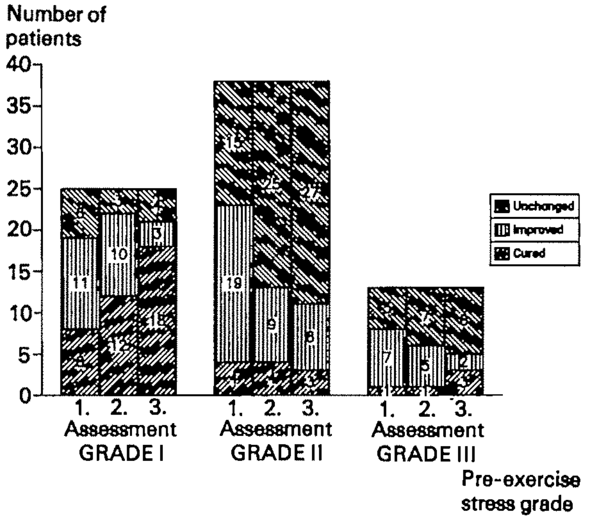

Fig. 1 Subjective results at the 3 assessments 0, 3 and 12 months after the 3-month pelvic floor exercise programme (y-axis) related to grade of incontinence before the exercises (x-axis)

significantly more women with grade I incontinence were cured. One year after completing the exercise programme 72% of the women (18/25) with grade I, 8% (3/38) with grade II, and 23% (3/13) with grade III incontinence were cured. The cure rates for grades II and III were not significantly different.

One year after completion of the exercise programme 24 patients (30%) were cured and 13 (17%) were so improved that they did not require surgery. Thus 47% of patients avoided surgery.

During the 1-year follow-up period 11 more patients (18%) were cured. Eleven of the 13 patients who were cured at the first assessment remained cured and 2 reported grade I incontinence but did not require surgery at the time of the last assessment. Of the 37 patients who had improved at the first assessment, 1/3 moved to the cured group and 1/3 to the unchanged group during the follow-up period. Of the 26 patients in the unchanged group at the first assessment, 2 were cured and 1 improved at the last assessment (Fig. 2).

The pelvic floor exercises also had a positive effect on nocturia, frequency and urge incontinence, since 40%, 66% and 32% respectively were cured at the first assessment.

Analyses of the influence of "patient variables" on the "result variables" were performed for each follow-up. The results at the first assessment are shown in Table 2. The same variables were found to be related either as a tendency or significantly at the following assessments. Patients who were more than 10% overweight had a significantly higher stress grade before the exercises than did those patients whose weight was normal. The same was seen after the exercises. However, a rate of 58% cured or improved in the overweight group was not significantly different from 67% in the normal weight group. Only 7 patients had been operated on previously. Their post-exercise stress grade and incidence of urge incontinence were significantly

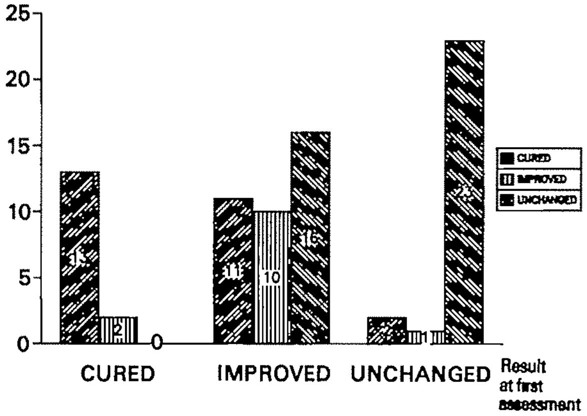

Fig. 2 Number of patients cured, improved and unchanged 12 months after the exercises (y axis) grouped according to subjective outcome at the first assessment (x axis).

Table 2 Relation between Patient Variables and Result Variables at First Assessment

	Result variables				
Patient variable	*Stress grade*	*Subjective result*	*Urge incontinence*	*Frequency*	*Nocturia*
> 10% over weight	$P=0\ 01$	NS	NS	NS	NS
Previous surgery	$P=0\ 025$	NS	$P=0.03$	NS	NS
Positive hormone status	NS	$P=0\ 01$	NS	NS	NS
Cystocele/rectocele	NS	NS	NS	$P=0.02$	$P=0.04$

NS = Not significant.

higher than in the non-operated group, but no difference was seen in the subjective results of the 2 groups.

A positive hormone status gave a significantly better chance of cure (20% compared with 4% in the group with negative hormone status). Among the patients with cystocele or rectocele a significantly higher number complained of frequency and nocturia after the exercises compared with the patients whose pelvic examination was normal.

Neither CCU diagnoses, age nor any of the other "patient variables" were significantly related to the results.

Pad Test

A group of 24 patients performed a 24-h home pad test before and after the exercise programme. Variance components analyses were performed on the log-transformed test results. The average leakage before the exercises was 26.4 g (4.0–93.0) for grade I, 77.9 g (11.9–274.9) for grade II and 263.9 g (40.4–930.9) for grade III incontinence. Leakage was significantly different in the 3 stress grades ($P=0.002$).

The results before the exercises and at the first assessment afterwards for each stress grade are shown in Figure 3 and they objectively support the patient's subjective outcome. The cured patients "leaked" on average 5.8 g (0.9–20.5) after the exercises and their post-exercise leakage was independent of the stress grade before the exercises. In the improved group, leakage diminished after the exercises to 9.8 g (1.5–34.5), 28.9 g (4.4–102.1) and 97.9 g (15.0–345.6) on average for stress grades I, II and III respectively. The reduction was significant ($P=0.001$) and the same for all stress grades (average 63%). In the unchanged group the leakage was not significantly reduced from pre-exercise values.

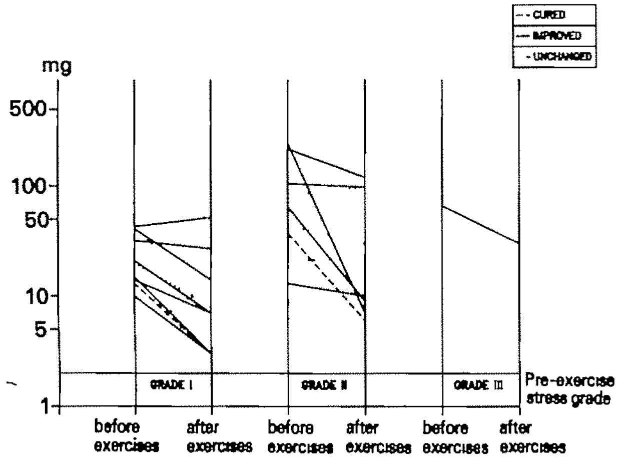

Fig. 3 Leakage during 24-h home pad test before and after the exercises in 24 patients (y axis) grouped according to grade of incontinence before the exercises (x axis).

APP Recordings

The APP recordings before and after exercise were evaluated in 61 patients. Variance components analysis of the maximum pressure (MP) revealed that the MP both at rest and at contraction of the pelvic floor was independent of the "patient variables" listed in Table 1.

Figure 4 outlines the MP at rest and at contraction before and after the exercises for the 3 subjective result groups. The pressure change differed significantly in the 3 result groups ($P=0.03$). In the cured group (13 patients) the average pressure increase was 2.9 cm H_2O (± 17.1) at rest and 5.1 cm H_2O (± 17.1) at contraction (the difference was significant at contraction). In the improved group (29 patients) the MP was the same before and after exercises at rest and the average increase was 1.7 cm H_2O at contraction; the difference was not significant. In the unchanged group (19 patients) the average decrease was 5.6 cm H_2O at rest and 3.4 cm H_2O at contraction.

The difference in MP from rest to contraction averaged 5.0 cm H_2O (± 10.3) before the exercises. This difference increased significantly ($P=0.03$) to 7.2 cm H_2O (± 10.3) in all subjective result groups after the exercises.

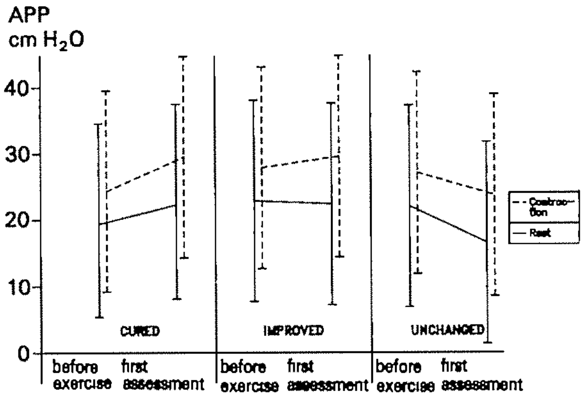

Fig. 4 Maximum pressure during APP recordings at rest and at contraction of the pelvic floor in 61 patients (y axis) before and after the exercise programme. The results are grouped according to subjective results at the first assessment (x axis).

Discussion

This study has shown that with an intensive pelvic floor exercise programme 47% of incontinent women may be cured or improved 1 year after completion of the exercises, thus avoiding surgery. These results are comparable to the findings of Henella *et al.* (1988), who found 65% of their patients cured or improved, and Wilson *et al.* (1987), who found 66% cured immediately after a hospital exercise programme. In the present study, 72% of patients with grade I incontinence were cured 1 year after the exercises. Differences in cure rates might be explained by differences in severity of incontinence and in follow-up time.

The results of the exercise programme, studied over a period of time, revealed that for patients who were cured immediately after the exercises the effect was permanent in 85% of cases. If subjectively improved at the first assessment, patients with grade I incontinence should continue to be followed up and encouraged to do further exercises at home or undergo a repeat hospital programme. Patients with grades II or III incontinence who were subjectively unchanged or subjectively improved at the first assessment derived only minor benefit from further exercises and should be offered surgery at this stage.

The exercise programme also had a positive effect on nocturia, frequency and urge incontinence. This could be partly explained by the effect on stress incontinence, since these variables were inter-related.

In a study of 14 patients, Henderson and Tailor (1987) reported better results from pelvic floor training in patients under 55 years of age compared with older patients. In our study, age did not influence the outcome.

Significantly more patients with a positive hormone status were cured by pelvic floor exercises. Heisterberg *et al.* (1987) found oestrogen treatment to be as beneficial for incontinence problems as pelvic floor exercises. Thus the combination of pelvic floor exercises and oestrogen treatment in patients with a negative hormone status might lead to better results.

The subjective results of the pelvic floor exercises were confirmed in patients who performed a 24-h pad test. Women who were cured "leaked" on average 5 g/24 h, which was equivalent to the leakage in a continent group, studied by Mouritsen *et al.* (1989).

In the present study the APP-recordings were used partly as a biofeedback method, since the patient could observe the registration curve and see if withholding resulted in contraction of the pubococygeus muscle by pressure increase. The APP recordings also served as an objective control of the effect of the exercises. The difference in maximum pressure at contraction and rest increased from 5.0 to 7.2 cm H_2O in the whole group, independent of subjective results. This indicates that all patients were able to contract the pelvic floor actively after the exercises. A higher MP at rest as well as at contraction was found in the cured group, which could be explained either as generally increased tonus or as a larger muscle mass of the pubococcygeus, in combination with improved active contraction of the muscle.

Only at contraction did the MP increase in the improved group, indicating that these patients could do the exercises as instructed but the effect was present only during active contraction. The group that was unchanged also failed to improve their MP.

It was concluded that at follow-up 1 year after completion of a 3-month hospital course of pelvic floor exercises, half of the patients were cured or improved and thus avoided surgery. Incontinence surgery should therefore always be preceded by at least 3 months of pelvic floor exercises.

All patients who were cured at the first assessment after the exercises were permanently cured. Patients who were improved at the first assessment should intensify the exercises, if they had mild incontinence, as 72% could expect to be cured with further training. Patients with moderate or severe incontinence and no immediate effect from the exercises should be offered surgery.

The training also had a positive effect on frequency, nocturia and urge symptoms. Patients with a positive hormone status and/or normal bodyweight benefited the most from pelvic floor exercises.

The subjective results were objectively confirmed by the pad test results. Anal pressure profilometry proved to be a valid method for instruction as well as control of the pubococcygeus muscle.

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Clam Enterocystoplasty in General Urological Practice

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Summary—A series of 45 patients (31 female) underwent clam enterocystoplasty for urgency and incontinence. The majority had detrusor instability. Prolonged conservative treatment had failed in all cases.

Improvement occurred in 71% and those younger than 30 years had better overall results; 29% remained incontinent, with 9% requiring a urinary diversion. Many patients did not achieve maximum benefit until 9 months post-operatively. Surgery had no statistically significant effect on any urodynamic parameter and post-operative complications were common.

The operation was performed in either the coronal (19) or the sagittal plane (26); this did not influence results. In general, surgery was found to be technically simpler in the sagittal group and it is recommended that this becomes the standard procedure. We feel that this operation involves major surgery and should only be offered with reluctance.

Primary detrusor instability is a common condition. The treatments available include bladder drill with additional behavioural and psychotherapeutic techniques, anticholinergic drugs, perivesical phenol injections (Blackford *et al.*, 1984), prolonged bladder distension (Dunn *et al.*, 1974) and bladder transection (Mundy, 1983). It is customary to use these treatments in order of increasing complexity. Whilst they may be effective, the response is often short-lived (Mundy and Stephenson, 1985). Much enthusiasm has recently been shown for augmentation cystoplasty of the "clam" type (Bramble, 1982; Mundy and Stephenson, 1985). We present our experience of this method with emphasis on patient selection, surgical technique and comparison of pre- and post-operative urodynamics.

Patients and Methods

Forty-five patients (14 male, 31 female, age range 19–79 years, median 45) underwent clam enterocystoplasty. The mean duration of symptoms was 8.2 years. All presented with urgency and frequency and 39 were incontinent. A small minority (Table 1) had a neurological disorder and may have had a neuropathic bladder; 44 patients underwent videocystometry (Bates and Corney, 1971) pre-operatively and 20 post-operatively; 44 patients had previously been treated with a variety of anticholinergic drugs. The one patient who did not receive drugs had spina bifida and had an endoscopic sphincterotomy and an indwelling catheter prior to his clam. Thirty-six patients had also been treated with other operative measures (Fig.).

Enterocystoplasty was eventually advised following the failure of other treatments to relieve symptoms which were intolerable or because of side effects. The path taken by each patient, via a

Table 1 Pre-operative Diagnosis

Symptoms	*Diagnosis*	
	Neurological disorder	*Idiopathic*
Incontinence	2 spina bifida	37 1 enuresis only
Others	1 spina bifida with catheter	2 frequency 2 conduits

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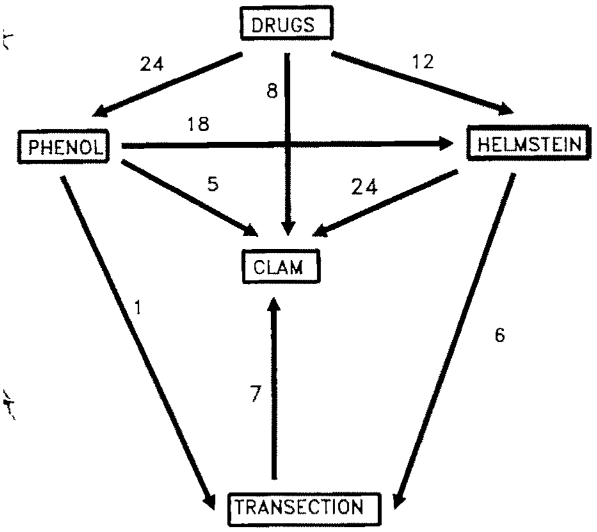

Fig. Path taken by patients through failed treatments to reach clam cystoplasty. Two patients diverted and undiverted between Helmstein and clam and 1 patient who had a sphincterotomy not shown for clarity

variety of failed treatments, to reach clam cystoplasty is shown in the Figure.

Pre-operative mechanical bowel preparation and intra-operative intravenous antibiotics were employed in all cases. The clam operation was performed in 19 patients in the coronal plane as described by Bramble (1982). However, in 26 patients the bladder was divided in the sagittal plane, from just above the intraureteric bar posteriorly to just above the bladder neck anteriorly.

A wide variety of absorbable sutures was used for the bladder/bowel anastomosis in this series. Distal ileum was employed in 40 patients and colon in 5. Post-operative cystograms were obtained in 28 patients prior to removal of their catheters.

Results

Mean follow-up was 20.3 ± 12.4 months with a minimum of 5 months, excluding 1 patient who died. Urinary catheters were removed at a median of 10 days (range 6–39). Hospital stay ranged from 4 to 39 days (median 11).

The clam performed sagittally had no adverse effect on in-patient stay, prognosis, symptoms, post-operative urodynamics or complications when compared with the traditional method. However, all surgeons who had used both methods found the sagittal procedure quicker and easier with less risk of disturbing the ureteric orifices. We found the incidence of early post-operative vesicoureteric reflux to be 36% in the sagittal group compared with 70% in the coronal group.

At the latest follow-up, patients gave a subjective assessment of success or failure of their clam. This assessment correlated well with symptom scores of frequency, nocturia, urgency and incontinence. Table 2 shows the overall results and a comparison of pre- and post-operative symptoms, with statistically significant improvements in all symptoms post-operatively.

Those who had good results were significantly younger than those with moderate or poor results ($P<0.005$ Mann-Whitney) with mean ages of 37 and 57 years respectively. Neither severity of symptoms nor the magnitude of any pre-operative urodynamic parameter had any influence on outcome. Surprisingly, all 4 patients with documented psychiatric illness had good results.

The 32 patients (71%) who improved following this operation experienced a reduction in their urgency and 31 patients (69%) were cured of their incontinence. Eight patients (18%) did not notice an improvement in their symptoms until as long as 9 months post-operatively; 14 patients remained incontinent, although in 4 this was barely perceptible. Twelve patients (29%) considered themselves symptomatically worse or no better, and 1 patient died. Four patients (9%) required urinary diversion for persisting symptoms; 2 patients had a TURP (transurethral resection of the prostate) pre-operatively and a further 3 males had bladder neck incisions post-operatively because of voiding dysfunction.

Table 2 Pre- and Post-operative Symptoms

	Pre-operative	*Post-operative*
Cured/much better		24 (53%)
Improved		8 (18%)
No better or worse		12 (27%)
Died		1 (2%)
frequency (×/day) (Mean ± SD)	17.2 ± 10.9	7.4 ± 5.0 $P<0.0005$*
nocturia (mean ± SD)	4.7 ± 4.0	2.0 ± 2.7 $P<0.0005$*
Urgency (total patients)	42 (93%)	11 (24%) $P<0.001$†
Urge incontinence (total patients)	40 (89%)	10 (22%) $P<0.001$†
Overall incontinence (total patients)	40 (89%)	14 (31%) $P<0.001$†

*Wilcoxon signed rank test
†Fisher's exact test

Voiding

Voiding was unsatisfactory in some patients, with voiding dysfunction replacing the symptoms of instability (Table 3). Five patients with voiding dysfunction were male, 4 needed to strain and 2 practised intermittent self-catheterisation (ISC). Fifteen patients (33%) practised ISC 1–6 times daily to void or to complete voiding.

One patient has an indwelling suprapubic catheter and another, who was constantly wet, required an early urinary diversion.

Urodynamics

Post-operatively, 15 patients (75%) had persistent detrusor instability (filling pressure > 15 cm H_2O), though 12 of these were improved symptomatically by the clam operation. There were no significant differences between pre- and post-operative data (Table 4). Only 3 patients with pre-operative detrusor instability had normal filling pressure post-operatively.

Complications

There were 2 early failures: 1 patient developed small bowel obstruction and following a second laparotomy became septicaemic and developed acute pancreatitis. She eventually died from multisystem failure 39 days post-operatively. One patient developed clinical peritonitis and at a second laparotomy there was no evidence of a leak or of peritonitis. Unfortunately, the pedicle of the 'clammed' ileum was avulsed. It was therefore resected and the bladder closed. This patient eventually had an ileal conduit because of severe symptoms. Apart from these 2 patients, all other early complications settled with conservative measures.

Table 3 Voiding Dysfunction

	Spontaneous voiding	*Strain to void*
ISC*	7 (15%)	8 (17%)
No ISC	25 (56%)	2 (4%)

*Intermittent self-catheterisation.

Table 4 Urodynamics

	Pre-op. *(n=44)* *mean ± SD*	*Post-op.* *(n=20)* *mean ± SD*
Bladder capacity (ml)	403.9 ± 194.2	471.1 ± 256.1
Residual volume (ml)	32.1 ± 78.7	140.5 ± 251
Filling pressure (cm water)	35.3 ± 22.7	28.5 ± 16.5
Voiding pressure (cm water)	42.2 ± 20.5	38.6 ± 18.7
Flow rate (ml/s)	14.6 ± 8.2	15.5 ± 8.0

Three of 44 patients were stable pre-operatively (filling pressure < 15 cm H_2O).

Recurrent urinary tract infections (UTI) occurred in 14 patients pre-operatively and 23 post-operatively. Post-operative UTI was more common in those who had to strain to void (90%) compared with spontaneous voiders (39%). Numbers were too small to be able to relate residual volume to these changes. However, all patients with residual volumes > 200 ml had recurrent UTI.

All patients had mucus in their urine and 23 of these found it sufficiently troublesome to require treatment with bladder washout or carbocysteine. This was unrelated to the incidence of UTI.

In addition to these, 26 post-operative complications occurred in 19 patients (Table 5).

Table 5 Post-operative Complications

Early UTI*	3	Urine leak	3
Incisional hernia	2	Prolonged ileus	4
Loin pain	3	Urethral stricture	2
Diarrhoea + vomiting	1	Deep venous thrombosis	1
Pulmonary embolism	1	Cardiac arrythmia	1
Peritonitis	1	Avulsed "clam"	1
Ejaculatory difficulty	1	Pancreatitis	1

*Urinary tract infection.

Discussion

These results demonstrate the continued value of the clam cystoplasty in detrusor instability. We have demonstrated a significant improvement in all symptoms in the medium term. The change in urodynamic parameters from unstable to stable seen elsewhere (Mundy and Stephenson, 1985) could not be demonstrated in this series, and apart from a trend towards increased residual volume, no significant change in urodynamic parameters was seen.

For many of our patients a good result was obtained at the expense of voiding dysfunction. It is obviously mandatory that this risk, and the possibility of intermittent self-catheterisation as an adjunctive treatment, should be explained to the patient beforehand. Recurrent UTI was more common post-operatively and seemed to be related to voiding dysfunction. This complication was largely relieved either by ISC and/or long-term prophylactic antibiotics. Historically, bladder neck incision was considered mandatory for male patients undergoing substitution cystoplasty. It has been performed only in a minority of our patients since most voided satisfactorily without urodynamic evidence of obstruction.

In a large proportion of our patients the clams were performed in the sagittal plane, and while this had no influence on results it did seem to make the operation technically simpler. We therefore recommend that this becomes the standard procedure. The large number of patients with early vesicoureteric reflux may be explained by the presence of a catheter balloon and the fact that cystograms were obtained only 7 to 10 days post-operatively. However, a proportion of patients continue to have reflux in the medium term as demonstrated during late urodynamic studies.

Our results are less satisfactory than those reported elsewhere (Bramble, 1982; Mundy and Stephenson, 1985) and the risk of serious complications is self-evident. This may partly be due to the fact that we relied on the patient's rather than the surgeon's assessment of success. More importantly, most of our patients underwent enterocystoplasty as a last resort after failure of all other forms of treatment. Nevertheless, we feel the operation should be reserved for patients with disabling symptoms which are refractory to other forms of treatment.

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The Significance of an Open Bladder Neck in Women

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Summary—The significance of an open bladder neck at rest has been investigated in 147 women presenting to a urodynamic clinic. The prevalence of this condition was 21%; there was an association with urethral sphincter incompetence but an open bladder neck was not diagnostic of it. It is suggested that the finding of an open bladder neck at rest during urodynamic investigation is of little consequence.

Genuine stress incontinence (GSI) is the most common cause of female urinary incontinence in young and middle-aged women. Continence is maintained at the level of the bladder neck but when this fails, the distal sphincter compensates (Turner-Warwick and Brown, 1979; Versi *et al.*, 1986, 1990). When the distal sphincter also fails, incontinence occurs (GSI).

Bladder neck incompetence under stress is a common finding even in women who are continent. In such cases the bladder neck is closed at rest and opens during a cough but fluid does not escape from the external urethral meatus as the distal sphincter mechanisms are still intact. This phenomenon is seen in 51% of otherwise urodynamically normal women presenting to a menopause clinic (Versi *et al.*, 1986). It has been observed even in asymptomatic women (Hilton and Stanton, 1983).

Some women have an open bladder neck at rest. Whilst this has been reported in various pathological states, especially those associated with a neuropathy, its significance is not clear in young asymptomatic women. In these women Chapple *et al.* (1989) reported a prevalence of 24% and suggested that women with an open bladder neck at rest were at greater risk of incontinence, especially after childbirth. They further suggested that the prevalence of an open bladder neck would be greater in the population at large if symptomatic women were also considered.

Given the above suggestion, the prevalence of an open bladder neck at rest is likely to be higher in patients presenting to a urodynamic clinic with symptoms of lower urinary tract dysfunction. The purpose of this study was to determine the prevalence of an open bladder neck at rest in these women and to assess its significance in relation to the prevalence of sphincter incompetence.

Patients and Methods

A total of 147 patients presenting to the urodynamic clinic with symptoms of lower urinary tract dysfunction were routinely assessed. This consisted of history, examination, urine testing for microscopy, culture and sensitivity, uroflowmetry and videocystourethrography (VCU). All patients were free of urinary tract infection.

During the VCU examination the bladder was filled with contrast medium (Isopaque) to capacity in the supine position. The patient's posture was then changed to the erect on a tilting table and the bladder neck was viewed in the oblique position with an image intensifier X-ray system. At this point the bladder neck was deemed to be either open or closed at rest by the investigator (E.V.).

The data were subjected to chi-squared analysis. The terms used conform to the standards of the International Conference Society (Abrams *et al.*, 1990).

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Results

The results of the urodynamic assessments are shown in Table 1. GSI was the most common condition and the prevalence of an open bladder neck at rest was 21.1% (±3.4%). Table 2 shows the relationship between the state of the bladder neck at rest and the state of the urethral sphincter. The probability of the patient having an incompetent sphincter was 0.613 if she had an open bladder neck at rest but only 0.362 if her bladder neck was closed at rest ($P<0.02$).

Table 1 Urodynamic Diagnoses

	Bladder neck at rest		
Diagnosis	*Closed*	*Open*	*Total (%)*
GSI	40	14	37
Mixed	2	5	5
DI	13	0	9
VD	8	0	5
Other	11	2	9
Normal	42	10	35
Total	116	31	100

GSI = Genuine stress incontinence; Mixed = GSI + DI; DI = Detrusor instability; VD = Voiding difficulties.

Table 2 Comparison of the State of the Bladder Neck at Rest and the Integrity of the Urethral Sphincter

	Bladder neck		
Sphincter	*Open*	*Closed*	*Total*
Incompetent	19	42	61
Intact	12	74	86
Total	31	116	147

Chi-squared = 6 0815, $P<0\ 025$.

Discussion

The overall prevalence of an open bladder neck at rest in patients presenting to the urodynamic clinic was 21%. These patients were statistically more likely to have sphincter incompetence than those with a closed bladder neck at rest but the difference was not great enough to allow a diagnosis to be made on the basis of the state of the bladder neck alone.

Women who have repeatedly undergone unsuccessful bladder neck surgery frequently have an open bladder neck at rest and in these women, GSI is often the diagnosis. However, in women who have GSI but have not previously had bladder neck surgery (as in this study), the association with an open bladder neck is less obvious.

None of the patients studied had an underlying neuropathy where it is known that the bladder neck can be open at rest and certainly opens during a detrusor contraction.

It has been suggested that an open bladder neck at rest may identify women who are at risk from subsequently developing GSI (Chapple *et al.*, 1989). The fact that the prevalence of an open bladder neck in the symptomatic urodynamic population was no different from that seen in a population of young women recruited from a family planning clinic (Chapple *et al.*, 1989) argues against such a hypothesis. On the contrary, the presence of an open bladder neck in a women who does not have a neuropathy, and who has not undergone bladder neck surgery, is probably not important. A longitudinal study of asymptomatic women with an open bladder neck at rest would help to answer this question.

On the other hand, continent women with an incompetent bladder neck on coughing are likely to be at risk of developing GSI. These women rely on their distal sphincter mechanisms and if these were to fail, incontinence would ensue (Versi *et al.*, 1990).

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Measurement of *in vivo* Urological Tumour Cell Kinetics Using Multiparameter Flow Cytometry

Preliminary Study

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Summary—The *in vivo* labelling of urological tumour cells using the S phase marker bromodeoxyuridine (BRdU) for histochemical studies is reported. The use of multiparameter flow cytometry (FCM) with BRdU labelling to study tumour proliferation offers significant advantages. It provides simultaneous measurements of the DNA ploidy (DI), the duration of the S phase (Ts), the potential doubling time (Tpot) and the total and aneuploid tumour labelling indices (LI) from a single specimen. Heterogenous tumour cell populations can be measured with high sensitivity. We report a preliminary study to evaluate the method in the measurement of the kinetics of transitional cell carcinoma of the bladder (TCCB).

Nineteen patients with TCCB, 1 with leukoplakia of the bladder, 2 with renal carcinoma, 1 with prostatic carcinoma and 1 with a squamous carcinoma of the penis were studied. Of the bladder tumours, 3 were aneuploid, DI = 1.32, 1.58 and 1.89. BRdU uptake was detected in all tumours. The median LI was 1.5% (range 0.5–10.0). In 15/19 tumours the labelling profile was satisfactory for calculation of the Ts and Tpot. The median Ts was 6.2 h and the median Tpot was 17.1 days.

This study demonstrates that measurement of multiple parameters of urological tumour proliferation *in vivo* is possible. These parameters require further assessment as indices of biological aggressiveness and clinical prognosis.

The *in vivo* study of human tumour proliferation kinetics has been handicapped by the need to use radioisotopes and to take multiple biopsies. The relationship of urothelial cell proliferation to the malignant process is not clearly understood. The use of multiparameter flow cytometry and *in vivo* bromodeoxyuridine labelling to measure *in vivo* kinetics is reported.

The DNA content of urological tumours may be a marker of biological aggressiveness (Barlogie *et al.*, 1983; Coon *et al.*, 1986; Fordham *et al.*, 1986; Frankfurt *et al.*, 1986; Hedley, 1989). The *in vivo* use of BRdU and immunohistochemistry to measure the BRdU labelling index (S phase fraction, SPF) has been described in the study of tumours of the renal pelvis and ureter (Nemoto *et al.*, 1989a), bladder (Nemoto *et al.*, 1988) and prostate (Nemoto *et al.*, 1989b). In each study it was concluded that higher SPF correlated with indices of biological aggressiveness.

The S phase fraction is a static measure of proliferation based on the counting of labelled cells, which under-uses the information available from *in vivo* labelling (Dolbeare *et al.*, 1983). The use of BRdU to measure the LI alone may have little advantage over *in vitro* studies. Better markers of urothelial tumour proliferation may help to determine prognosis, the likelihood of muscle invasion and hence the planning of follow-up and treatment. This study was undertaken to assess the *in vivo* measurement of bladder tumour proliferation kinetics by flow cytometry.

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Patients and Methods

The patients were selected on urographic and cystoscopic evidence of a bladder tumour, by urography of the renal tumours and by local biopsy of the prostatic and penile lesions. Each consented to receive a single intravenous bolus of 250 mg BRdU (Takeda, Japan) administered over 30 s in 10 ml saline, between 3 and 6 h prior to surgery. Resected tumour fragments were stored in 70% ethanol. Nuclear suspensions were obtained by digestion of tumour fragments in 8 ml porcine pepsin (Sigma, UK) solution in 0.1 M HCl (1.0 mg/ml) for 20 min at 37°C. Nuclei were resuspended in 3 ml 2 M HCl for 8 min at room temperature and then washed in fresh phosphate buffered saline (PBS). The concentration of nuclei was adjusted to 2,000,000/ml.

Nuclei were resuspended in a solution of 0.5 ml of 0.5% Tween 20 (Sigma UK) in PBS containing 2.5 µl of goat serum; 25 µl of anti-BRdU monoclonal antibody supernatant (Seralab, UK) were added. They were then washed and incubated in 0.5% Tween with goat serum and 25 µl of goat anti-rat antibody-FITC conjugate for 1 h at room temperature. Nuclei were then washed twice in PBS.

Nuclei were resuspended in 3 ml PBS containing 10 µg/ml of 1.0 mg/ml propidium iodide (Sigma). Analysis was carried out on an Ortho Systems 50-H Cytofluorograph. Excitation was at 488 nm with a 5 W Argon ion laser operating at 200 mW. Calibration was performed with fluorescent beads. Red gain was adjusted to collect the G1Diploid DNA peak at channel 200. Controls were normal human diploid colorectal mucosa. Green fluorescent light (FITC) was collected at 510–560 nm and red fluorescence (PI) above 620 nm. Data were collected by the computer in list mode and gated to exclude multiple nuclei. Data for 10,000 nuclei were collected from each specimen. Analysis was performed according to the method described in detail by Begg *et al.* (1985) and Wilson *et al.* (1988).

In this model the potential doubling time, Tpot, is related to the total labelling index (LI) and the S phase duration (Ts) by the formula

$$\text{Tpot} = (\text{Ts}/\text{LI}) \times 0.8$$

The Tpot, which is the theoretical rate of tumour growth when there is no cell loss, must be distinguished from the observed volume doubling time, Vd, which is affected by cell loss due to exfoliation and necrosis (Steel, 1977). The Ts is estimated from the relative movement (RM) of the labelled S phase population through the cycle since the bolus injection, assuming even S phase distribution of label at T0. Examples of the DNA and (BRdU vs DNA) histograms obtained in this study are shown in Figure 1.

Wax-embedded sections of labelled tumours were stained by a standard avidin-biotin-peroxidase technique (Hayashi *et al.*, 1988) using the same anti-BRdU monoclonal antibody. This enabled the distribution of stained cells to be analysed. An example of a BRdU-labelled bladder tumour is shown in Figure 2. The BRdU-labelled cells stain darkly with peroxidase label.

Results

Bladder tumours

Nineteen patients with superficial transitional cell tumours and 1 with leukoplakia undergoing transurethral tumour resection were studied (B1–B20); 18 tumours yielded an analysable DNA profile; 15 were diploid and 3 were aneuploid (Table). Of the 2 failures, B3 was very necrotic, while satisfactory profiles could not be obtained from B4 for reasons which are not clear.

BRdU uptake was detected in all specimens. The median LI of the 19 bladder tumours was 2.5% (mean 2.2, range 0.5–10.0). In 15 tumours the profile was satisfactory for calculation of the Ts and Tpot. The median Ts was 6.2 h (mean 6.2, range 3.5–9.7) and the median Tpot was 17.1 days (mean 19.4, range 3.6–40.0). In the case of the aneuploid tumours, Ts and Tpot calculations were based on the aneuploid labelling index, which is composed purely of the tumour cell population and excludes stromal cells.

Patients B1–B11 underwent a check cystoscopy at 3-monthly intervals in the first year. Follow-up of these patients was undertaken for up to a mean period of 9 months. B3 was immediately treated with radiotherapy. B4 and B8 developed recurrences widely within 3 months and failed to respond to Adriamycin. Patients B12 to B20 have not yet undergone sufficient follow-up.

Histochemical staining of representative TCCB blocks demonstrated clearly the uptake of BRdU in S phase cells. These were randomly distributed throughout the tumours. There was no discernible pattern to the distribution of staining.

Renal and other tumours

BRdU appears to be incorporated reliably into all types of tumours of urological importance so far studied. Satisfactory (BRdU vs DNA) histograms

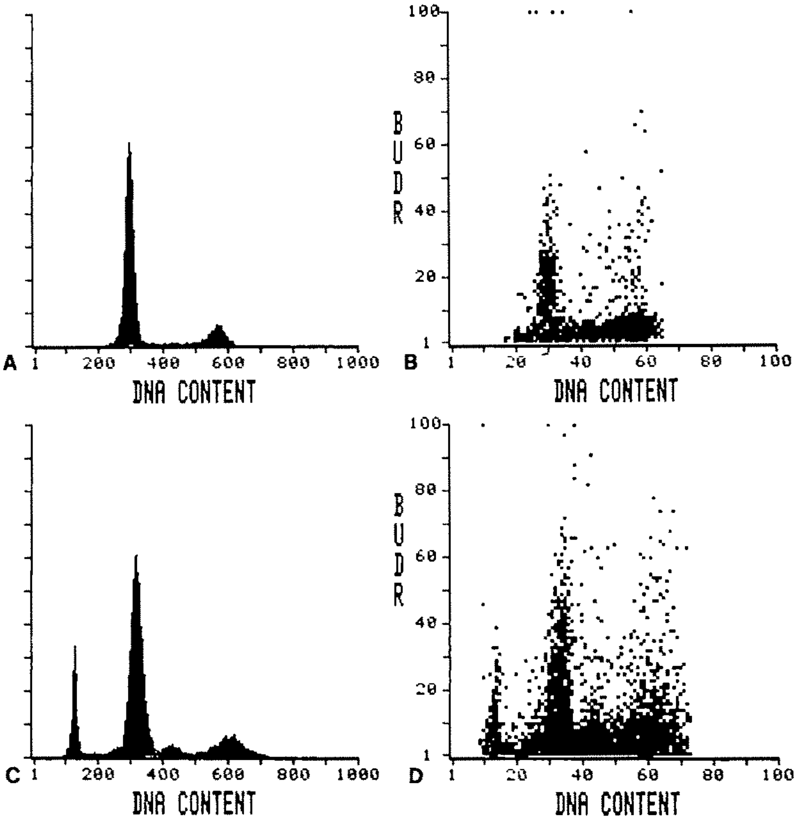

Fig. 1 Representative histograms of a diploid bladder tumour (A and B) and an aneuploid renal carcinoma (C and D) A and C are the DNA profiles (cell number vs DNA content). B and D are the BRdU profiles (BRdU content on the y axis vs DNA content on the x axis). Each tumour was excised 5 h after labelling. A large number of labelled cells in each tumour have already divided and entered the G1 phase of the next cell cycle.

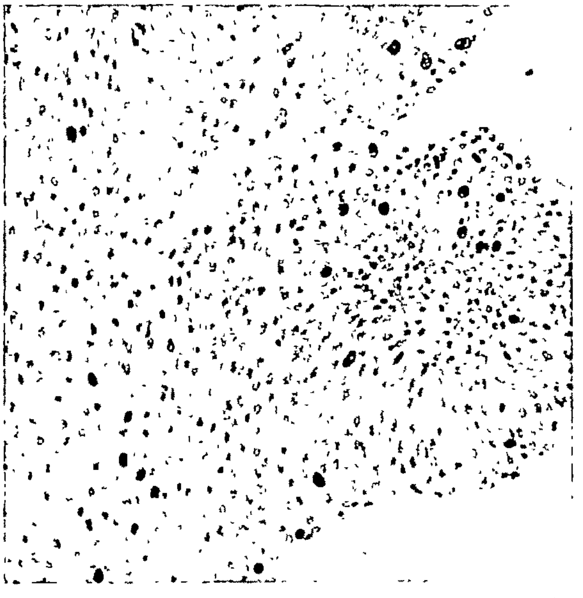

Fig. 2 Transitional cell carcinoma of the bladder showing BRdU-labelled tumour cells stained with peroxidase. S phase cells are irregularly distributed throughout the tumour. (× 16).

were derived from each of the 4 extravesical tumours analysed (Table).

Discussion

Transitional cell carcinomas of the bladder run an unpredictable clinical course and the mechanisms which determine their progression are not fully understood. One hypothesis is that malignant potential is related to the rate of cell proliferation. In the past it has been difficult to test this simple hypothesis at the cellular level. Tritiated thymidine, the past keystone of kinetic studies, is unsuitable for clinical use. *In vitro* studies using 3H-Thymidine or BRdU labelling provide at best a static index of proliferation. Ploidy studies have been handicapped by problems with artefact produced by the disaggregation of wax-embedded material, more so than in ethanol-fixed or fresh tissue. Measurements of the S phase fraction by monoparameter FCM are an indirect index of proliferation. Consequently, the contribution of cell turnover to malignancy in transitional carcinomas is not fully understood.

Table Results

*Patient no.**	*Pathology*	*DNA Index*	*Total LI (%)*	*(Range)*	*Ts (h)*	*Tpot (days)*	*F/U*
B1 (n=3)	pT1G2	1.00	0.8	(0.5–1.0)	4.2	17.5	–
B2 (n=2)	pT1G2	1.00	1.0	(0.3–1.7)	4.3	14.3	–
B3 (n=1)	pT2G3		10.0				–
B4 (n=2)	pT2G2		4.4	(3.9–4.7)			+++
B5 (n=4)	pT1G2	1.00	2.9	(1.3–5.2)	3.5	4.0	–
B6 (n=4)	pT1G2	1.89	4.0	(2.4–4.0)	6.5	5.4	–
B7 (n=2)	pT1G2	1.00	1.1	(0.5–1.6)	9.7	29.4	–
B8 (n=5)	pT1G2	1.00	2.0	(0.9–3.9)	7.4	12.3	+++
B9 (n=2)	pT1G1	1.00	5.1	(2.9–7.3)			–
B10 (n=1)	pT1G2	1.00	2.9				+
B11 (n=1)	pT1G2	1.00	1.1		6.6	20.0	–
B12 (n=1)	LKP	1.00	2.0		8.3	13.9	
B13 (n=1)	pTaG2	1.00	1.8		6.0	11.1	
B14 (n=1)	pT1G2	1.00	0.6		6.2	34.4	
B15 (n=2)	pT2G3	1.58	5.7	(5.5–6.0)	6.2	3.6	
B16 (n=1)	pTaG1	1.00	0.5		6.0	40.0	
B17 (n=1)	pT1G1	1.00	0.6		6.1	33.9	
B18 (n=1)	pT1G2	1.32	1.5		4.9	10.9	
B19 (n=1)	pT3G2	1.00	1.4		7.2	17.1	
B20 (n=1)	pTaG1	1.00	0.8		8.9	37.1	
K1 (n=1)		2.00	6.6		7.1	4.5	
K2 (n=1)		1.50	1.9		11.9	18.0	
P1 (n=1)		1.00	1.9		9.0		7.7
S1 (n=1)		1.00	1.9		6.6		11.5

*n = number of specimens studied from each tumour. Where multiple results were obtained, LI and Ts data are the mean values F/U (±) is the extent of recurrence by 6 months follow-up, where follow-up data are so far available B = Bladder. K = Renal. P = Prostate S = Squamous tumour of the penis. LKP = Leukoplakia with no frank malignancy

Using multiparameter FCM, ploidy profiles and data describing the rate of cell proliferation can be obtained from a single biopsy. Large numbers of nuclei are counted with accuracy and data can be obtained in one working day. The safety and efficacy of *in vivo* tumour labelling with BRdU has been established in a number of tumour types (Wilson *et al.*, 1988; Rew *et al.*, 1990). The technique may be of value in the study of urological tumours, with careful adjustment of the preparation conditions. TCCB is a valuable model for the study of human tumour cell kinetics. It is readily accessible and the rate of cell exfoliation may be quantified in the urine. Recurrences are sufficiently frequent to make serial calculations of both the Tpot and the Vd possible.

In order to obtain good nuclear suspensions for analysis, care should be taken to avoid diathermy artefact during tumour resection. Urothelial tumour cells appear to be very sensitive to standard pepsin disaggregation methods. Overdigestion yields unsatisfactory DNA profiles. Our tumours were unpredictable in their sensitivity to the pepsin and to DNA denaturation with 2M HCl as described. Although BRdU labelling was demonstrated and measured in all tumours, more detailed analysis of the cell cycle phases was not possible in 4 tumours because of repeatedly wide coefficients of variation in the peaks of the DNA histograms.

The timing of the pre-operative BRdU bolus is important. Between 3 and 8 h is optimum. This interval ensures S phase labelling with sufficient movement of labelled cells through the cell cycle to allow the Ts to be calculated (Wilson *et al.*, 1988), while ensuring that the majority of the labelled cells are still in the S phase at the time of resection. A bolus injection is preferable to a continuous infusion of the drug because it provides a true pulse label to the replicating DNA. No acute events attributable to BRdU have been observed and no long-term side effects of the drug at this dosage have been observed or reported.

The low labelling index of TCCB increases the error range in the calculation of the Ts and Tpot from the BRdU histogram as compared with rapidly proliferating tumours. Low S phase labelling increases the potential error in the calculation of the Ts and Tpot because interpretation of the histogram and the setting of gates is operator-dependent. Some labelling of stromal cells may also occur. It is not possible to distinguish diploid tumour from stromal nuclei in the DNA histogram. These will affect the calculation of the total tumour LI. Flow cytometry and histochemical studies of labelled cells should be considered as complementary procedures, since the tissue distribution of the BRdU label cannot be assessed in nuclear disaggregates.

Studies of colorectal and head and neck tumours (Wilson *et al.*, 1988; Rew *et al.*, 1990) have suggested that the Ts and LI are independent variables, so that the rate of proliferation and the labelling index are not synonymous. Our preliminary data suggest that there may be a wide range of proliferation rates in bladder tumours, which may turn out to reflect differences in tumour behaviour, time to recurrence and clinical outcome. Bromodeoxyuridine is reliably taken up into a wide range of human solid tumours and proliferating epithelial tissues for multiparameter studies. Our early studies on extravesical tumours reported here suggest that urological tumours will prove to be no exception, and these now merit further assessment.

Multiparameter flow cytometry is an evolving technique with a range of applications in the study of tumour biology. It can be used to quantify cell protein content, including oncoproteins (Watson *et al.*, 1986; Czerniak *et al.*, 1987; Dent *et al.*, 1989). The availability of monoclonal antibodies against cell proteins (topoisomerases, p 170 glycoprotein) will facilitate the development of predictive bioassays to assess tumour resistance to cytotoxic agents.

The technique of FCM/BRdU labelling is a significant advance in the study of urological tumour cell kinetics. We conclude that prospective multiparameter FCM studies of urological tumour kinetics are possible. The value of *in vivo* kinetic data as prognostic and therapeutic indicators for chemotherapy and radiotherapy should now be assessed in larger series with adequate follow-up.

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Detection of Human Papillomavirus DNA in Cancer of the Urinary Bladder by *in situ* Hybridisation

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Summary—The association of the human papillomavirus (HPV) with cancer of the urinary bladder was assessed by *in situ* hybridisation using probes selective for HPV types 6/11 and 16/18 DNA. No hybridisation signal was detected with the type 6/11 probe on 100 formalin-fixed, paraffin-embedded bladder tumours sampled. However, when the same samples were hybridised with the HPV type 16/18 DNA probe, 11 of 66 (16.6%) papillary and 1 of 10 (10%) solid transitional cell carcinomas gave positive signals. These results suggest the involvement of HPV in cancer of the bladder, although the frequency of multiple HPV types in these tumours is uncertain.

While viral studies on mammalian urothelium have shown an association between the bovine papillomavirus (BPV) and cancer of the bladder in cattle (Olson *et al.*, 1965; Jarrett, 1987), the evidence for HPV involvement in urinary bladder cancer in man is less clear. Sixty types of HPV are known to infect man and although most of these proliferations are benign, some may convert to malignancies (Syrjanen, 1990). This conversion is related to HPV type: for example, in the genitourinary tract, HPV types 6 and 11 are most commonly associated with genital warts (condylomata acuminata), whereas types 16 and 18 are associated with more severe dysplasias and carcinomas (zur Hausen, 1987). Genital condylomata can extend to the urethra and urinary bladder and also remain in close association with cancer of the bladder (Murphy *et al.*, 1983; Walther *et al.*, 1986; Shirai *et al.*, 1988). The presence of HPV antigen in cancer of the bladder has previously been established (Bryant *et al.*, 1987). However, although HPV DNA types 6 and 11 have been identified in condylomata and cancers of the bladder and urethra (Del Mistro *et al.*, 1988; Querci Della Rovere *et al.*, 1988; Mevorach *et al.*, 1990; Wilson *et al.*, 1990), the presence of HPV types 16 and 18 in cancers of the urinary bladder has yet to be substantiated.

In order to investigate further the role of HPV in these tumours, 100 paraffin sections of urinary bladder tumours were analysed for the presence of HPV types 6/11 and 16/18 DNA using a non-isotopic *in situ* hybridisation technique. The findings showed the presence of HPV type 16/18 DNA in transitional cell carcinomas of the bladder, and the significance of these results is discussed.

Materials and Methods

A total of 100 transurethrally resected urinary bladder samples were fixed in 10% formalin and embedded in paraffin wax. Sections (3 μm) were stained with haematoxylin and eosin and examined microscopically (Table). The samples were then examined for HPV DNA by *in situ* hybridisation. Formalin-fixed and paraffin-embedded genital condylomata and positive HPV 16 control slides (Bio-Nuclear Services, Reading) were used as controls.

Probes

The DNA probes studied were plasmid pUC19 (Gibco Ltd, Paisley) for use as a negative control probe, and HPV DNA types 6b, 11, 16 and 18, kindly donated by Professor H. zur Hausen and Dr E. M. de Villiers, DKFZ, Heidelberg, Germany. The probes were biotinylated with biotin 11-dUTP (Gibco Ltd) using a nick translation kit (Gibco Ltd)

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Table *In situ* Hybridisation of Urinary Bladder Samples using HPV DNA Probes

Histopathology	*No of patients*	*HPV 6/11*	*HPV 16/18*
Papillary TCC	66	—	11
Solid TCC	10	—	1
Mixed papillary/solid TCC	2	—	—
Squamous cell carcinoma	3	—	—
Adenocarcinoma	4	—	—
Undifferentiated carcinoma	7	—	—
Dysplasia	3	—	—
Benign	5	—	—

TCC—transitional cell carcinoma

and following the recommended protocol. Unincorporated dNTPs were separated from the biotinylated DNA by the spun column technique (Maniatis *et al.*, 1982).

The concentration of each of the stored biotinylated probes was 10 ng/µl. For use, the HPV type 6/11 DNA probe cocktail was prepared by adding 40 µl each of HPV types 6 and 11 biotinylated probes to 2 ml of hybridisation buffer [2 × SSC (1 × SSC is 150 mM sodium chloride, 15 mM tri-sodium citrate), 5% (w/v) dextran sulphate, 0.2% (w/v) milk powder, 50% (v/v) formamide]. This was sufficient to treat 25 paraffin sections. The HPV type 16/18 probe was prepared similarly.

Pre-treatment

Paraffin sections were cut on to single-well slides (C. A. Hendley, Loughton) coated with 3-aminopropyltriethoxysilane (Sigma Chemical Company, Poole) as previously described (Burns *et al.*, 1987), and incubated for several days at 56°C to ensure maximum adhesion. The sections were dewaxed in xylene for 2 × 5 min and washed in absolute alcohol for 2 × 5 min. The sections were then hydrated through to distilled water and digested in 1% (w/v) diastase (Sigma) for 30 min at 37°C. Following a rinse in distilled water, each slide was incubated in 100 µl of proteinase K (Sigma) at a concentration of 100 µg/ml in 20 mM calcium chloride, 20 mM Tris hydrochloride, pH 7.4, for 1 h at 37°C, rinsed in distilled water, dehydrated in alcohol and air dried for 1 h.

Hybridisation

The slides were placed on a tray, 75 µl of each probe mixture were applied to duplicate sections, and covered with Gelbond (Miles Laboratories, Slough) with the hydrophobic side down. The slides were incubated on a metal tray at 90°C for 6 min and then transferred to a humidified tray overnight at 42°C. Following incubation, the Gelbond was removed and the slides rinsed in 2 × SSC for 2 × 20 min at room temperature and then in 0.1 × SSC containing 0.1% (v/v) Triton X100, 0.04% (w/v) magnesium chloride, at 42°C for 30 min.

Detection

To each slide was added an aliquot of 0.01% (v/v) streptavidin (Dako Limited, High Wycombe) in TBS buffer, pH 7.6 [50 mM Tris, 150 mM sodium chloride, 2 mM magnesium chloride, 0.1% (w/v) bovine serum albumin] and the slides incubated at room temperature for 30 min. Following a rinse in TBS buffer for 5 min, the slides were incubated in an aliquot of 0.1% (v/v) biotinylated alkaline phosphatase (Dako) in TBS buffer for 30 min at room temperature. The slides were rinsed in TBS buffer, washed for 5 min in veronal acetate buffer, pH 9.2 (30 mM sodium acetate, 30 mM sodium barbitone, 100 mM sodium chloride, 50 mM magnesium chloride) and developed for 60 min in a filtered solution of 0.05% (w/v) fast red TR, 0.05% (w/v) naphthol AS BI phosphate (pre-diluted in 100 µl dimethylformamide) and 0.024% (w/v) levamisole in veronal acetate buffer. The slides were rinsed in water, counterstained in Mayer's haemalum, washed in water for 5 min and mounted in Apathy's medium.

Results

Of the 100 urinary bladder samples analysed by *in situ* hybridisation, no signal was detected using the HPV type 6/11 DNA probe. However, positive hybridisation signals were detected in 12 samples when the sections were hybridised with the HPV type 16/18 DNA probe. Of these, 11 of 66 (16.6%) were papillary and 1 of 10 (10%) was a solid transitional cell carcinoma. Hybridisation using the pUC19 probe and all other samples were negative (Table). The positive hybridisation signals were seen as red, water-insoluble precipitates confined to isolated nuclei in well differentiated areas of the tumours. In the papillary tumours, the signals were primarily found in the clear, koilocyte-like or adjacent cells (Fig. 1). However, the positive signal in the solid carcinoma was found in isolated tumour cells and not in the koilocyte-type cells found in adjacent urothelium (Fig. 2). Background staining due to the affinity of avidin for glycogen (Grody *et al.*, 1987) was eliminated by pre-treatment of the sections with diastase. Over-development of the colour reaction can produce a high level of

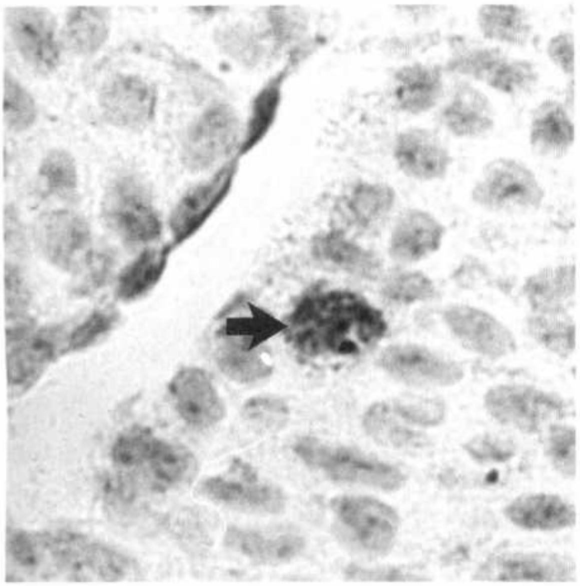

Fig. 1 *In situ* hybridisation of a low grade papillary transitional cell carcinoma showing an isolated nucleus (arrowed) positive with the HPV 16/18 biotinylated DNA probe. (Fast red-naphthol capture method × 920).

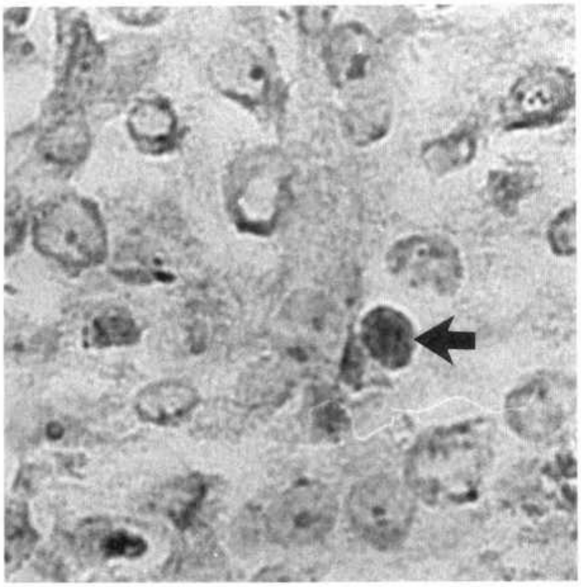

Fig. 2 High grade solid transitional cell carcinoma showing nuclear positivity (arrowed) for HPV 16/18 DNA using *in situ* hybridisation and a biotinylated probe. (Fast red-naphthol capture method × 920).

background staining, but this was controlled by monitoring the reaction after the first 30 min.

Incidentally, using the immunocytochemical method previously described (Bryant *et al.*, 1987), 6 of the 12 tumours (50%) showing positive hybridisation signals with the HPV 16/18 DNA probe were also positive for PV structural antigen.

Discussion

Cancer of the urinary bladder is one of the most common malignancies in males in the occidental population and several factors have been implicated in the development of these tumours (Morrison, 1984; Hartge *et al.*, 1985). The association of HPV with pre-malignant and malignant lesions of epithelium has long been recognised and such lesions are found throughout the genitourinary tract (Syrjanen, 1990).

The presence of condylomata in the bladder is well documented (Walther *et al.*, 1986; Shirai *et al.*, 1988). Because these lesions are typical of HPV infection (Krzyzek *et al.*, 1980), their presence suggests that infection by HPV may lead to carcinoma of the bladder. However, while there was no evidence to suggest the presence of condylomata in the patients in this study, the question arises as to whether HPV is regularly associated with other tumours of the urinary bladder. This study has shown that all of the samples analysed for HPV type 6/11 DNA were negative. This supports the concept that HPV types 6 and 11 are closely associated with benign lesions. In contrast, HPV types 16/18, which are more commonly associated with severe dysplasias and carcinomas (zur Hausen, 1987), were identified in 16.6% of papillary and 10% of solid transitional cell carcinomas. Previous studies have shown that while cancer of the bladder has been associated with HPV types 11 (Querci Della Rovere *et al.*, 1988) and 16 (Kitamura *et al.*, 1988; D. J. McCance, unpublished observations), several studies have failed to demonstrate other HPV types in them (Green *et al.*, 1981; Kahn *et al.*, 1986; T. Kitamura, personal communication). Furthermore, HPV type 6 has been identified in a papillary transitional cell carcinoma of the urethra but not in a histologically similar papillary cancer of the bladder in the same patient (Mevorach *et al.*, 1990). It has also been suggested that since HPV-associated lesions have been identified in the male urethra (Melchers *et al.*, 1989), bladder tumours obtained by transurethral resection could include HPV-infected urethral cells. In fact, bladder cancer patients have been found to have a higher incidence of HPV infection than the general population (Hartveit and Maehle, 1989). However, although this study has shown the presence of HPV in transitional cell carcinomas of the bladder, further studies will be necessary in order to assess more fully the role that these and other HPV types may have in the genesis of these tumours.

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The Human Prostate Gland: A Histochemical and Immunohistochemical Study of Neuropeptides, Serotonin, Dopamine β-hydroxylase and Acetylcholinesterase in Autonomic Nerves and Ganglia

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Summary—Different regions of the prostate gland, namely the prostatic capsule, peripheral prostate, and proximal and distal central prostate, were obtained from 5 patients with carcinoma of the bladder and studied histochemically and immunohistochemically to localise acetylcholinesterase (AChE)-, dopamine β-hydroxylase (DBH)-, serotonin- and peptide-containing nerves. Autonomic ganglia were found in all regions of the prostate studied. The greatest number of ganglia contained AChE and neuropeptide Y (NPY) followed (in decreasing order) by DBH; [Met]enkephalin (mENK) and [Leu]enkephalin (lENK); calcitonin gene-related peptide (CGRP) and vasoactive intestinal polypeptide (VIP); and serotonin, but not somatostatin. The greatest density of nerve fibres was found in the proximal central prostate, followed by the anterior capsule and distal central prostate, with the least in the peripheral prostate. The greatest number of nerve fibres contained ACh and NPY, followed in decreasing order by VIP and DBH; lENK, serotonin and CGRP; mENK; substance P and somatostatin. The functions of the neurotransmitter substances in the human prostate remain to be elucidated.

The prostate gland plays an important role in reproduction and is also the site of benign and malignant neoplasms. Benign prostatic hyperplasia is prevalent over the age of 40 years and as many as 29% of men of this age may undergo prostatectomy because of bladder outlet obstruction (Glynn *et al.*, 1985).

There is controversy over the gross anatomy of the prostate. However, the current consensus supports the anatomical studies of McNeal (1972), who divided the prostate gland into central and peripheral zones based on both morphological and embryological criteria. Despite the marked clinical importance of this organ, little information is available on its physiological functions and few reports have appeared on the subject of its innervation.

The smooth muscle of the mammalian prostate gland receives dual sympathetic and parasympathetic innervation (Brushini *et al.*, 1978; Vaalasti *et al.*, 1980; Gilpin *et al.*, 1983) via the hypogastric and pelvic nerves. Small amounts of prostatic fluid are continuously secreted (Smith and Lebeaux, 1970). Parasympathetic stimulation increases the rate of secretion and under sympathetic stimulation, prostatic fluid is expelled into the urethra (Smith and Lebeaux, 1970; Brushini *et al.*, 1978).

The human prostate gland is also supplied by peptide-containing nerves: vasoactive intestinal polypeptide (VIP), [Met]- and [Leu]enkephalin (mENK and lENK), neuropeptide Y (NPY), substance P (SP), somatostatin (SOM), but not calcitonin gene-related peptide (CGRP)-containing nerves have been described (Vaalasti *et al.*, 1980; Gu *et al.*, 1983a, b; Adrian *et al.*, 1984). In addition, serotonin (5-hydroxytryptamine; 5-HT)-containing glandular endocrine-paracrine cells have been described in the human prostate (Di Sant'Agnese *et al.*, 1985).

No previous studies have comprehensively stud-

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ied the distribution of "classical" and putative neurotransmitters with regard to the degree of regional prostatic heterogeneity. Thus in the present study, the distribution of neuropeptides, namely, VIP, mENK, lENK, NPY, SP and CGRP, the amine 5-HT and the enzymes dopamine β-hydroxylase (DBH) (a marker for adrenergic nerves) and acetylcholinesterase (AChE) has been investigated in several regions of the prostate gland.

Materials and Methods

Patients and tissue collection

Specimens of prostatic tissue were obtained from 5 patients undergoing radical cystoprostatectomy for carcinoma of the bladder, none of whom had received prior radiotherapy (mean age 66.2 ± 5.98 years). These patients had no symptoms suggestive of bladder outlet obstruction, although benign prostatic hyperplasia was present.

Tissues were collected from the operating theatre and transferred immediately to ice-cold isotonic buffered Hank's solution.

To investigate potential differences in the innervation of the prostate, several regions of the gland were sampled; namely anterior capsule, peripheral zone and central zone, which was further subdivided into 2 areas: near the bladder neck (proximal) and near the verumontanum (distal) (Fig. 1).

Histology

Cryostat sections of all of the above-mentioned regions of the prostate were stained with haematoxylin and eosin to assess any morphological abnormalities.

Histochemistry

Cryostat sections of the different regions of the prostate were fixed in 10% formalin and 1% calcium chloride. AChE was localised according to the method of Karnovsky and Roots (1964). The tissues were pre-incubated in 1×10^{-5} M tetraisopropylpyrophosphoramide for 20 to 30 min to inhibit the activity of non-specific cholinesterase, before transferring to the incubating medium containing the substrate acetylthiocholine iodide (Sigma). The tissues were viewed using light microscopy and areas were photographed on Ilford FP4 film.

Immunofluorescence

The tissues were fixed in 4% paraformaldehyde in phosphate-buffered saline (PBS) for 2 h and washed thoroughly with 7% sucrose (ANALAR-Sigma) in PBS containing 0.01% sodium azide (BDH) and stored for at least 24 h at 4°C. An indirect fluorescence technique (Coons *et al.*, 1955) was used to investigate the presence of immunoreactive nerves to VIP (Radioimmunoassay (UK) Ltd), SOM (Dakopatts), mENK (Peninsula), lENK (Peninsula), CGRP (Cambridge Research Biochemicals (UK) Ltd), 5-HT (Immuno Nuclear Corporation), DBH (Eugene Tech International Inc), in cryostat sections (10 μm) of the prostate. The cryostat sections of the tissues were incubated for 18 h at room temperature, with polyclonal antibody raised in rabbit, dilution 1:200 for each antibody except VIP (dilution 1:1000). The sites of antigen-antibody binding were revealed by incubating for 1 h at room temperature with goat anti-rabbit IgG conjugated to fluorescein isothiocyanate (FITC) (Miles-Yeda Ltd) dilution 1:100. The preparations were washed, mounted with phos-

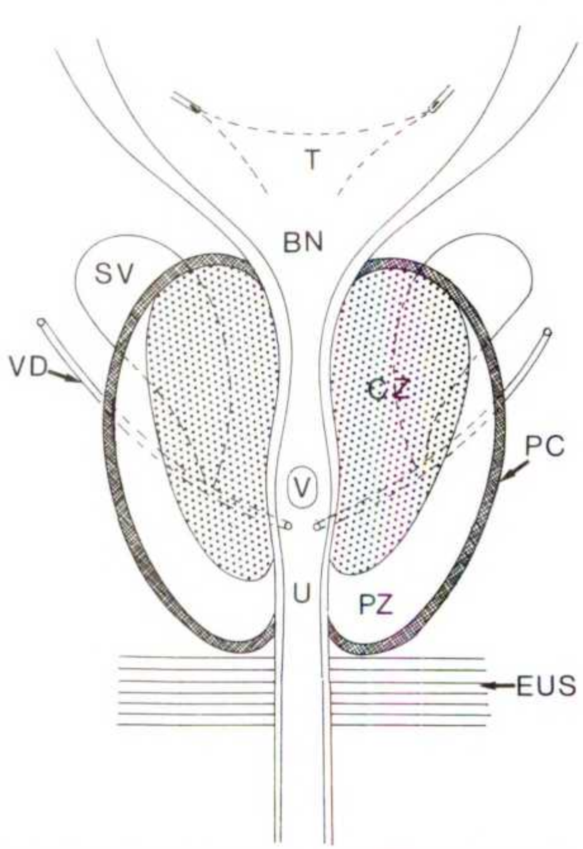

Fig. 1 Schematic diagram of the adult human prostate showing the central zone (CZ), peripheral zone (PZ) and prostatic capsule (PC). Seminal vesicles (SV) and vasa deferentia (VD) fuse to form ejaculatory ducts to open alongside the verumontanum (V) in the urethra (U). The trigone (T), the bladder neck (BN) and the external urethral sphincter (EUS) are also shown.

phate-buffered saline and glycerol (Cityflour; City University) and viewed using a Zeiss microscope equipped for viewing FITC fluorescence and phase-contrast microscopy. Selected areas were photographed on HP5 film. For controls the tissues were incubated with antibody inactivated by the addition of excess antigen (10 nmol of antigen to 1 nmol of respective antisera).

Quantitation

The density of nerves containing neuropeptides, 5-HT, DBH and AChE was classified subjectively into 6 groups by the authors (Table).

Results

Histology

Haematoxylin and eosin stained sections of the different regions of the prostate showed that the anterior capsule was composed entirely of smooth muscle fibres and fibro-elastic connective tissue (Fig. 2A). The peripheral zones contained predominantly smooth muscle fibres, collagen and connective tissue, with few glandular alveoli and ducts (Fig. 2B).

The different regions within the central prostate contained numerous mature fibroblasts in loose transparent connective tissue, numerous alveoli, ducts and fewer smooth muscle fibres (Fig. 2C) when compared with the anterior capsule and peripheral prostate.

Intrinsic ganglia were found in all areas of the prostate studied. In each region, 1 to 8 ganglia, each containing 3–59 nerve cell bodies (diameter 25–40 µm), were found (Figs. 3–5A, 6A, C, 7A). The greatest number of nerve cell bodies was found in the proximal and distal regions of the central prostate followed by the anterior capsule, with the least in the peripheral prostate.

Histochemistry and Immunohistochemistry

The intramural autonomic ganglia in all regions of the prostate contained 5-HT, DBH and AChE, and all of the peptides studied (Figs 3A, 4B, 5A, 6A, C, 7A), with the exception of SOM.

The greatest number of nerve cell bodies contained AChE and NPY, followed (in decreasing order) by DBH; mENK and lENK; CGRP and VIP; and 5-HT. 5-HT immunoreactivity was also observed in cells in the prostatic glandular epithelial layer. Most of these 5-HT-immunoreactive cells had dendritic processes that extended between the epithelial cells. Within the prostatic ganglia, nerve fibres were found to ramify in between or to encircle the nerve cell bodies (Figs 3–6A). These nerve fibres contained 5-HT, DBH and AChE and most of the peptides studied, the exceptions being SOM and SP.

The distribution and density of nerve fibres found in the prostate gland are summarised in the Table. In all regions of the prostate studied, most of the nerve fibres were found around the glandular alveoli in the smooth muscle of the interstitial tissue (Figs. 3B, 4B, C, 5B, 7B, C). They were found singly (Figs 3B, 4B, 5C, 7C) and/or in nerve bundles (Figs 4C, 5B, 6B, 7C), running predominantly along the longitudinal axis of the smooth muscle fibres. The greatest density of nerve fibres were AChE-positive and immunoreactive to NPY, followed in decreasing order by VIP and DBH; lENK, CGRP and 5-HT; mENK; SP; and SOM. CGRP-, SP- and 5-HT-immunoreactive nerves were found predominantly in nerve bundles and only VIP- and NPY-immunoreactive nerve fibres extended between the alveolar secretory cells.

There was a variation in the density and location of the different types of nerves studied (Table). Generally, the greatest density of nerves was found in the proximal (near the bladder neck) central

Table Density of Neuropeptide-, 5-HT-, DBH- and AChE-containing Nerve Fibres in the Anterior Capsule, Peripheral Prostate, and Proximal and Distal Central Prostate

Prostatic area	VIP	SP	SOM	mENK	NPY	CGRP	lENK	5-HT	DBH	AChE
Anterior capsule	+++	+	Oc	+	+++++	++ NB	+++	–	++++	+++++
Peripheral prostate	+++	+	–	–	+++++	++ NB	–	++++ NB	+	+++++
Proximal central prostate	++++	++ NB	–	+++	+++++	+++	+++ NB	+++	+++++	+++++
Distal central prostate	+++	Oc	Oc	+	+++++	+	++	+	+++	+++++

– = absent, + = sparse; ++ = sparse/moderate, +++ = moderate, ++++ = moderate/dense; +++++ = dense; NB = nerve bundle; Oc = occasionally.

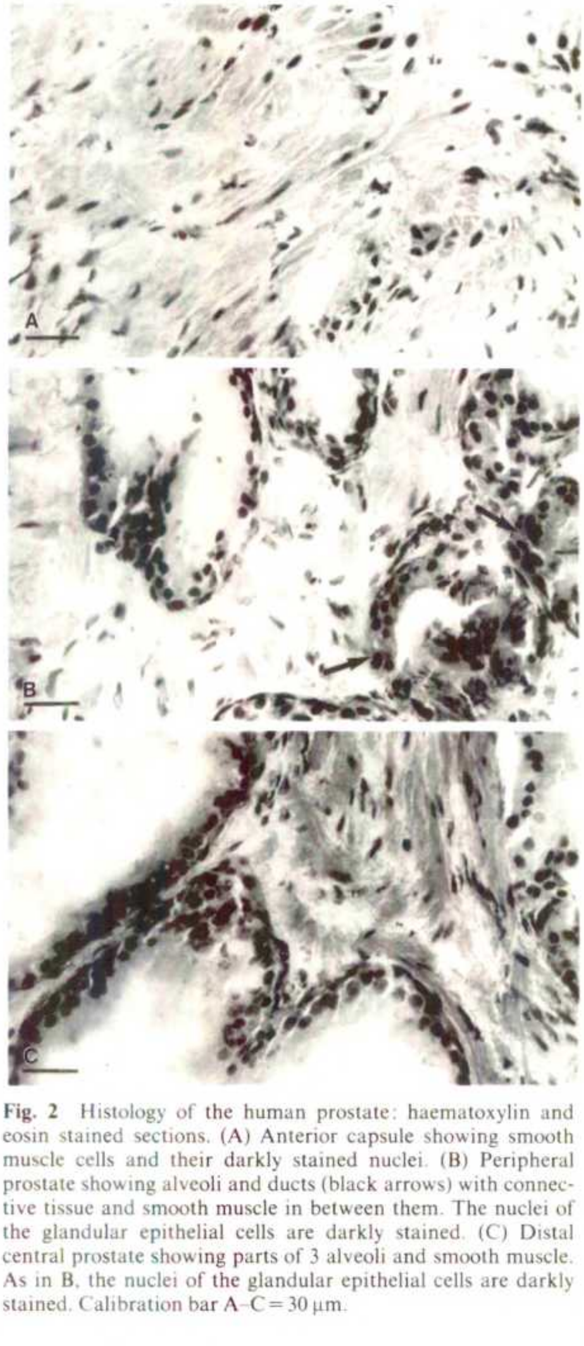

Fig. 2 Histology of the human prostate: haematoxylin and eosin stained sections. (A) Anterior capsule showing smooth muscle cells and their darkly stained nuclei. (B) Peripheral prostate showing alveoli and ducts (black arrows) with connective tissue and smooth muscle in between them. The nuclei of the glandular epithelial cells are darkly stained. (C) Distal central prostate showing parts of 3 alveoli and smooth muscle. As in B, the nuclei of the glandular epithelial cells are darkly stained. Calibration bar A–C = 30 μm.

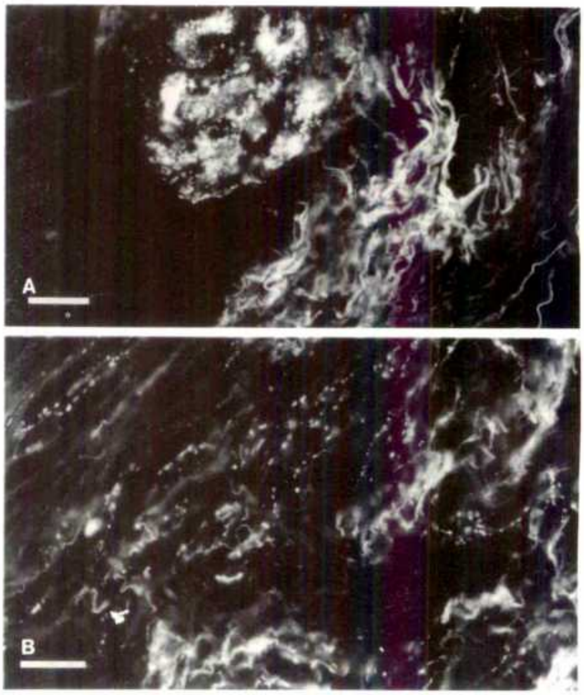

Fig. 3 VIP immunoreactivity in sections of the human prostate. (A) A ganglion containing VIP-immunoreactive nerve cell bodies is seen in the anterior prostatic capsule. Collagen fibres are brightly autofluorescent. (B) Fine, varicose VIP-immunoreactive nerve fibres are seen in the smooth muscle of the proximal central prostate. Calibration bar A, B = 30 μm.

prostate, followed by the anterior capsule and the distal central prostate, with the least in the peripheral prostate. Within each region of the prostate studied, AChE-positive, NPY- and to a large extent VIP-immunoreactive nerves were uniformly distributed (Table). In the anterior capsule there were a few fibres showing immunoreactivity for SP and mENK, a low density of CGRP-immunoreactive nerves, a moderate density of VIP- and lENK-immunoreactive nerves, and a fairly dense distribution of DBH-immunoreactive nerves. 5-HT-immunoreactive nerves were absent.

In the peripheral prostate, SOM-, mENK- and lENK-immunoreactive nerves were absent. This region had a few SP- and CGRP-immunoreactive nerves, with a low number of DBH-immunoreactive nerves, a moderate number of VIP-immunoreactive fibres, but the greatest density of 5-HT-immunoreactive nerves compared with other prostatic regions. In the proximal central prostate there was an absence of SOM-immunoreactive nerves, but there were more SP-, mENK-, CGRP- and DBH-immunoreactive nerves, while in the distal central prostate there were fewer lENK-, CGRP-, DBH-, 5-HT- and SP-, but more VIP-containing nerves compared with other prostatic regions. SOM-immunoreactive nerves were only occasionally observed in the anterior capsule and distal central prostate (Table).

NPY-, VIP-, CGRP- and DBH-immunoreactive nerves were also observed on the adventitial medial

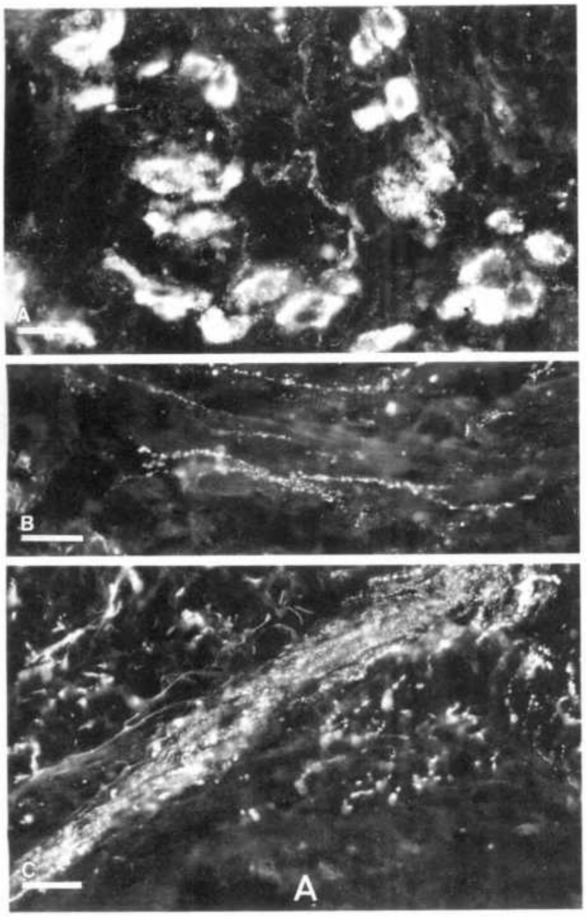

Fig. 4 NPY immunoreactivity in sections of the human prostate. (A) A ganglion containing brightly fluorescent NPY-immunoreactive nerve cell bodies and a few nerve fibres is seen in the distal central prostate. (B) Varicose NPY-immunoreactive nerve fibres are seen running along the longitudinal axis of smooth muscle fibres of the anterior prostatic capsule. (C) A large nerve bundle containing NPY-immunoreactive nerve fibres is seen adjacent to an alveolus (A) in the proximal central prostate. Calibration bar A–C = 30 μm.

border of blood vessels in all regions. When the prostatic tissues were incubated with antibody inactivated by the addition of excess antigen, fluorescent nerves immunoreactive to neuropeptides 5-HT and DBH were absent.

Discussion

The present study shows that the human prostate gland has a complex neuronal composition and is supplied by nerves containing at least 9 different types of transmitters, although some may be co-localised. There have been few reports on the autonomic ganglia in the human prostate. Ganglia containing AChE and small intensely fluorescent cells have been described on the prostatic capsule, while AChE-positive and VIP-immunoreactive nerve cell bodies have been reported in the prostate (although the specific location of these was not described) (Dunzendorfer *et al.*, 1976; Gosling and Thompson, 1977; Vaalasti and Hervonen, 1980; Gu *et al.*, 1983a,b). The present study shows for the first time that there is a widespread distribution of autonomic ganglia within the human prostate, since they were found in the prostatic capsule, peripheral prostate, and proximal (near the bladder neck) and distal (near the verumontanum) central prostate. We have also shown that in addition to AChE- and VIP-containing nerve cell bodies, the neuronal cell bodies within ganglia also contained NPY-, lENK-, mENK-, CGRP-, SP-, 5-HT- and DBH-immunoreactive nerve cell bodies and fibres.

No studies have yet been carried out on the function of the intrinsic neurones in the prostate. However, by analogy with studies of the intrinsic

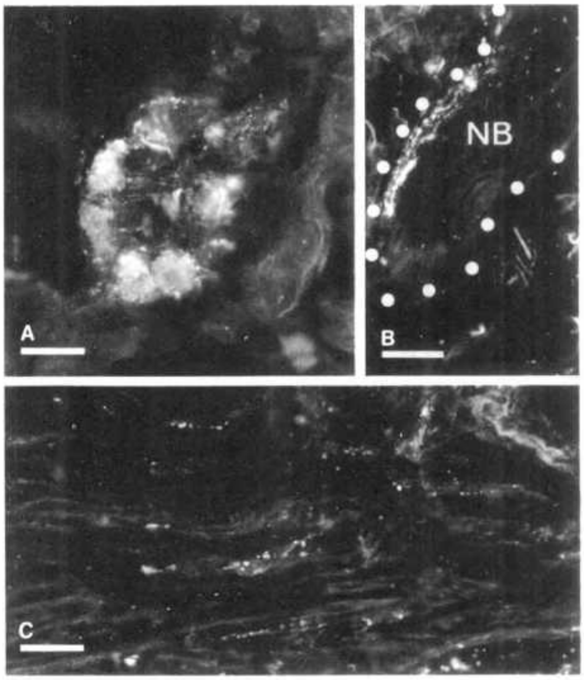

Fig. 5 CGRP immunoreactivity in sections of the human prostate. (A) A ganglion containing CGRP-immunoreactive nerve cell bodies is seen in the distal central prostate. (B) A nerve bundle containing a few CGRP-immunoreactive nerve fibres is seen in the distal central prostate. Most of the nerve fibres in the nerve bundle (NB) are non-fluorescent (outlined in white dots). (C) Fine, varicose CGRP-immunoreactive nerve fibres are seen in the smooth muscle of the distal central prostate. Calibration bar A–C = 30 μm.

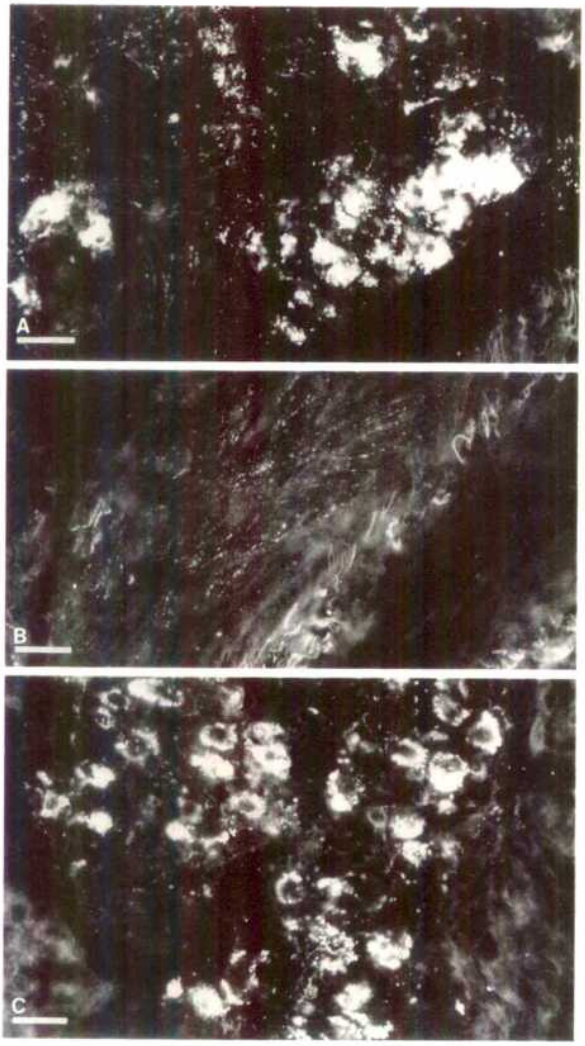

Fig. 6 mENK and lENK immunoreactivity in sections of the human prostate. (A) A ganglion containing mENK-immunoreactive nerve cell bodies and nerve fibres is seen in the distal central prostate. (B) A large nerve bundle containing lENK-immunoreactive nerve fibres is seen in the distal central prostate. (C) A ganglion containing lENK-immunoreactive nerve cell bodies and a few nerve fibres is seen in the distal central prostate. Calibration bar A–C = 30 μm.

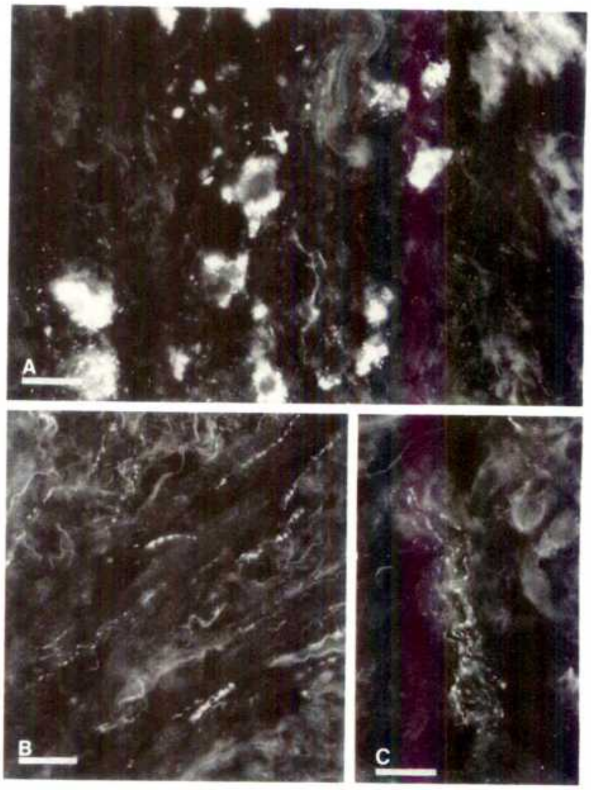

Fig. 7 DBH immunoreactivity in sections of the human prostate. (A) A ganglion containing DBH-immunoreactive nerve cell bodies and a few fluorescent nerve fibres is seen in the proximal central prostate. Most of the nerve fibres in this ganglion are non-fluorescent. (B) Fine, varicose, DBH-immunoreactive nerve fibres are seen in the smooth muscle of the proximal central prostate. (C) A nerve bundle containing DBH-immunoreactive nerve fibres is seen in the proximal central prostate. Calibration bar A–C = 30 μm.

ganglia in other organs (Burnstock *et al.*, 1987a,b), it is likely that they play an integrative and/or modulatory role in prostate activity rather than acting as simple relay stations.

In the present study, nerve fibres containing neuropeptides, 5-HT, DBH and AChE have been found in the different regions of the prostate studied. However, there was a great variation in the density of these nerves in different regions, with no clear pattern of innervation related to specific types of nerves with specific prostatic region. Generally, the greatest density of the different types of nerves appeared to be in the central prostate near the bladder neck, with the least in the peripheral prostate, but with similar densities in the anterior capsule and distal central prostate.

The bladder neck and proximal urethra are generally more densely innervated by different types of nerves than the bladder detrusor muscle, external urethral sphincter and distal urethra (Ek *et al.*, 1977; Gosling *et al.*, 1977; Andersson *et al.*, 1978; Kluck, 1980; Klarskov *et al.*, 1983; Moss, 1988; Crowe and Burnstock, 1989). In view of the close proximity of the proximal central prostate to the bladder neck, it is perhaps not surprising that this region of the prostate is the most densely innervated.

There was some degree of prostatic hyperplasia in the prostates from the patients (mean age 66 years) used in this study, since this is a prevalent feature of this age group. Prostatic hyperplasia usually arises in the segment surrounding the urethra and pre-prostatic sphincter. As the hyperplasia develops, the normal prostate is pushed out to the periphery and forms a false capsule (Tanagho, 1984). Thus the peripheral zone used in this study represents "normal" prostate. It is unclear why this region contained the lowest density of nerves compared with other prostatic regions. It is possible that atrophy of some types of nerves has occurred, with compensatory growth of new nerves in other regions.

Previous studies have reported that the human prostate gland is innervated by cholinergic parasympathetic nerves (Dunzendorfer *et al.*, 1976; Gosling and Thompson, 1977; Vaalasti and Hervonen, 1980), adrenergic sympathetic nerves (Gosling and Thompson, 1977; Vaalasti and Hervonen, 1980) and nerves containing the peptides VIP, ENK, NPY, SP and SOM (Gu *et al.*, 1983a,b).

Functional and receptor binding studies have suggested that the adrenergic nerves of the prostate act via α_1-adrenoceptors to maintain bladder outlet resistance (Lepor and Shapiro, 1984; Hedlund *et al.*, 1985). Further, phenoxybenzamine and prazosin (α-adrenoceptor antagonists) significantly diminished prostatic resistance, resulting in increased urinary flow rates in men with bladder outlet obstruction due to benign prostatic hyperplasia (Caine *et al.*, 1978; Gerstenberg *et al.*, 1983; Hedlund *et al.*, 1983).

While AChE staining cannot be regarded as specific for cholinergic nerves (Burnstock and Robinson, 1967; Chubb *et al.*, 1980), it may give some indication of the presence of nerves using acetylcholine. The function of cholinergic nerves in the human prostate remains uncertain. Although numerous cholinergic receptors have been found in the prostate (Lepor and Shapiro, 1984; Lepor and Kuhar, 1984; James *et al.*, 1989), prostatic specimens of adenomatous tissue and non-hyperplastic tissue do not respond to muscarinic receptor agonists, acetylcholine and carbachol (Lepor and Shapiro, 1984). However, the prostatic capsule showed a marked response to cholinergic stimulation and it was suggested that the capsule was not derived from the prostate, but represented the outer circular muscle layer of the urethra (Caine *et al.*, 1978). It has been suggested that the cholinergic nerves in the prostate have a secreto-motor function and increased muscle sensitivity to sympathetic stimulation, an effect that occurs in sexual arousal prior to the onset of ejaculation (Loewe, 1938; Dziuk and Norton, 1962; Brushini *et al.*, 1978; Gosling, 1979).

The distribution of the neuropeptide-, 5-HT-, DBH- and AChE-containing nerves was similar in the human prostate, *i.e.* they were found in the smooth muscle, surrounding the glandular ducts, alveoli and nerve cell bodies of intrinsic ganglia. At present little is known of the possible function of the neuropeptides and 5-HT in the human prostate. However, it is possible that the neuropeptides have a neurotransmitter/neuromodulator and/or trophic function. 5-HT has been localised in human prostatic endocrine-paracrine cells (Di Sant'Agnese *et al.*, 1985; this study). It has been suggested that 5-HT is concerned with the production and control of prostatic secretion, which would be compatible with the location of prostatic endocrine-paracrine cells, *i.e.* found in the prostatic epithelial layer of glandular ducts and alveoli.

In previous studies it has been shown that neuropeptides coexist within the "classical" autonomic nerves, *i.e.* VIP is present in cholinergic nerves and NPY in adrenergic nerves (Lundberg, 1981; Lundberg and Tatemoto, 1982). Similarly, SOM, lENK and mENK have also been demonstrated in some populations of adrenergic nerves (Schultzberg *et al.*, 1980; Viveros and Wilson, 1983).

Although the functions of VIP and NPY in the human prostate are unknown, in the human bladder VIP has a dose-related prolonged relaxatory effect and a powerful vasodilator effect (Larsson *et al.*, 1981; Said, 1984), while NPY is known as a pre- and post-junctional modulator of adrenergic transmission: NPY has been implicated in the central regulation of bladder activity. Since both VIP- and NPY-immunoreactive nerves have been found in the prostate and urethra (Crowe and Burnstock, 1989; this study), which are closely related both anatomically and embryologically (Raz *et al.*, 1973), it is possible that the NPY-immunoreactive nerves may function to maintain urethral outlet resistance during bladder filling, while VIP-immunoreactive nerves may function antagonistically and decrease urethral resistance during micturition. Since DBH, CGRP, NPY and VIP have been found around blood vessels, it is likely that these nerves also regulate local blood flow.

The endorphins and enkephalins are important in some pain mechanisms (Terenius, 1978). Although mENK- and lENK-immunoreactive nerves were absent in the peripheral prostate, they were present in the other regions of the prostate studied.

The enkephalins are thought to inhibit synaptic transmission in both the central and peripheral nervous systems and are thought to affect both the pre- and post-synaptic sites (North *et al.*, 1979; Yang and Costa, 1982; Yang *et al.*, 1983; Pittam *et al.*, 1987). It has been shown that in sympathetic ganglia (Hervonen *et al.*, 1981; Dalsgaard *et al.*, 1982; Vaalasti *et al.*, 1986), both mENK and lENK inhibit cholinergic transmission presynaptically. A similar function may occur in the human prostate, since there is a dense population of AChE-positive nerves.

CGRP- and SP-immunoreactive nerves have been associated with sensory nerves and are thought to be involved in the processing of pain and in axon reflexes causing vasodilatation in skin (Hökfelt *et al.*, 1980). Sensory nerves would be important in acute prostatitis, during which pain is the most common feature (Dunzendorfer *et al.*, 1976), but is absent in benign nodular hyperplasia or carcinoma of the prostate. It has been suggested that functional abnormality of sensory nerves within the prostate gland is an important contributory factor to the genesis of detrusor instability.

Thus the present study has revealed that the innervation of the human prostate is more complex than was hitherto believed, but further experiments are required to clarify the coexistence of neurotransmitter substances and their roles in the biology of the prostate.

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Hospitalisation of Prostatic Cancer Patients Undergoing Orchiectomy

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Summary—We report our experience with 100 orchiectomies for advanced prostatic cancer in hospitalised patients. Approximately 60% of the patients required hospitalisation for additional treatment and investigation of complications due to their disease at the time of orchiectomy. In 51 cases the orchiectomy was combined with transurethral resection of the prostate (TURP); 37 patients had pathological levels of serum creatinine and 17 had pathological dilatation of the upper urinary tract, 6 of whom required a nephrostomy catheter. Because of anaemia on admission, 21 patients received a peri-operative blood transfusion. Two patients had significant post-operative bleeding, 2 developed a wound infection and 1 had a deep thrombophlebitis.

The patients' mean age was 76.4 years and the period of hospitalisation ranged from 3 to 150 days with peaks at 3 and 8 days. The most important reason for prolonged hospitalisation was social problems.

It was concluded that many patients who were hospitalised as a direct consequence of their prostatic carcinoma would have been in hospital for a similar period regardless of the method of hormonal manipulation used. Because so many patients have other reasons for hospitalisation, or require additional surgical procedures such as TURP, the true average cost of orchiectomy for advanced prostatic cancer is difficult to determine.

Most prostatic cancers are androgen-dependent and since the work of Huggins *et al.* (1941), castration has had a central place in the treatment of advanced prostatic cancer. The effect of medical castration with LH–RH analogues has been likened to that of surgical castration (Turkes *et al.*, 1987).

In most countries orchiectomy has been carried out on hospitalised patients, while medical castration has been introduced as an out-patient procedure or even administered at home. In the course of their disease, however, most prostatic cancer patients need hospitalisation for reasons other than orchiectomy, such as revision of the bladder outlet, treatment of ureteric obstruction, *etc.* We have made a retrospective study of patients undergoing orchiectomy during hospitalisation, with emphasis on whether castration might equally well have been performed as an out-patient procedure.

Patients and Methods

The study was based on 100 orchiectomies dating from 1988 and earlier, according to the operation records.

All available information in the patients' case notes was evaluated, such as applications for admission, initial case notes, laboratory results, discharge reports, operation reports, anaesthetic charts, pathological examinations, X-rays and scintiscans, nurses' reports, ward charts and out-patient notes.

The annual number of operations varied from 19 in 1985 to 35 in 1986. Staging was based on digital rectal palpation.

The patients' ages ranged from 56 to 90 years. Most were between 70 and 85 years old (mean 76.4) (Fig. 1).

Classification

One patient had a T1 tumour, 26 T2, 38 T3 and 35 patients had T4 tumours.

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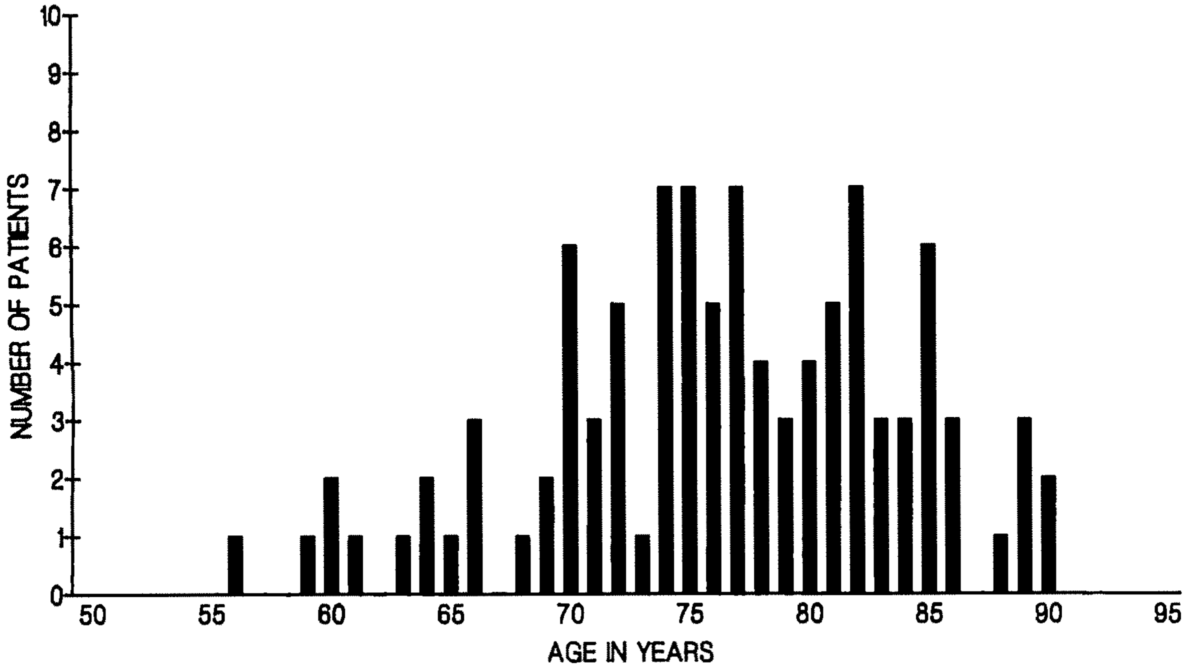

Fig. 1 Age distribution of 100 patients undergoing orchiectomy for prostatic cancer.

Ten patients had highly differentiated tumours; in 73 cases they were moderately differentiated and in 17 they were poorly differentiated.

Distant metastases had been detected in the skeleton of 50 patients, 5 had secondary lung tumours on chest X-ray and 8 had metastases in various sites such as the brain and regional and distant lymph nodes.

Serum creatinine levels were above normal in 37 patients and 17 had pathological dilatation of the upper urinary tract.

Results

Surgical treatment

A total of 49 patients underwent elective orchiectomy as the only surgical procedure; 29 were admitted primarily for transurethral resection of the prostate because of infravesical obstruction, but orchiectomy was performed as well. In 22 cases orchiectomy was combined with TURP, although this was not planned beforehand. On questioning, the patients admitted to having obstructive voiding problems and since they "were already at the operation table" the urologist decided to revise the bladder outlet in the same procedure.

Additional treatment and investigations

Six patients were given a pre-operative blood transfusion because of anaemia; 15 needed a postoperative blood transfusion, 5 following orchiectomy and 10 after combined orchiectomy and transurethral prostatectomy. None had significant bleeding during surgery. All had a low haemoglobulin concentration on admission and this fell below what was thought to represent a critical level during surgery.

Six patients required a nephrostomy catheter because of tumour obstruction of the distal ureters. One patient sustained a pathological fracture of the shaft of the femur on the day of admission and was treated conservatively with bone traction.

Eleven of the 49 patients who underwent elective orchiectomy alone were considered to need hospitalisation because of various complications from their disease.

Hospitalisation

The length of hospitalisation for the 100 patients who underwent orchiectomy for advanced carcinoma of the prostate varied from 3 to 150 days. The distribution was bimodal, with peaks at 3 and 8 days (Fig. 2). Some patients had an extremely

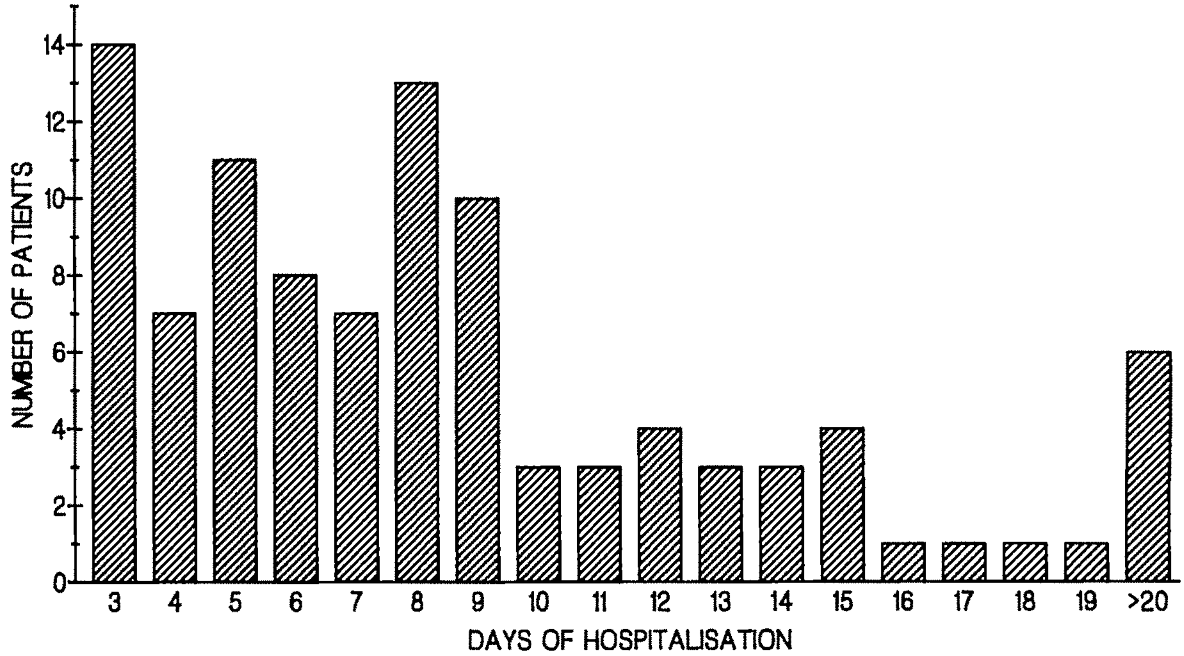

Fig. 2 Duration of hospitalisation for 100 patients undergoing orchiectomy; 51 also underwent TURP.

prolonged period of hospitalisation for reasons unrelated to either the orchiectomy or the TURP. Mean periods of hospitalisation are therefore not presented.

Most of the 49 patients who underwent orchiectomy alone left hospital within 5 days. The distribution was unimodal with a peak at 3 days (Fig. 3). For the 51 patients treated by orchiectomy and TURP in the same procedure, the period of hospitalisation also showed a unimodal distribution with a peak at 8 days (Fig. 4).

Complications

Two patients developed a wound infection. One had undergone orchiectomy only, the other both orchiectomy and transurethral prostatectomy. Their period of hospitalisation was 10 and 15 days respectively. Both had a suppurating fistula from the operation wound for a considerable time after discharge. Two patients had significant post-operative bleeding after orchiectomy and 1 developed deep thrombophlebitis of a lower limb.

Reasons for prolonged hospitalisation

It was found that 35 patients waited more than 1 day before operation (mean delay 5.8 days). In 17 cases the delay was due to administrative reasons, 7 patients had to await the result of biopsies, and on 4 occasions orchiectomy was postponed because the patient needed a nephrostomy. In 3 cases surgery was postponed because of pre-operative transfusions and in 3 other cases the reasons were neurological disorders and Hodgkins' disease requiring closer examination. One patient had a pathological limb fracture on the day of admission.

Forty patients experienced a post-operative delay before discharge and 25 could not return to their homes because of social problems. In most cases the patients' relatives were exhausted and the community home nursing system had collapsed while the patient was in hospital. Other reasons for post-operative delays were a pathological limb fracture in 1 patient and insertion of nephrostomy catheters in 6 patients because of obstruction of the distal ureters by tumour. There was no difference in the mean age of patients whose hospitalisation exceeded 10 days and those who were admitted for less than 10 days. Apart from the patients with complications, prolonged hospitalisation was related neither to the orchiectomy nor to the transurethral prostatectomy.

Discussion

The stage of the disease in our patients reflects the indications for orchiectomy, which we believe are

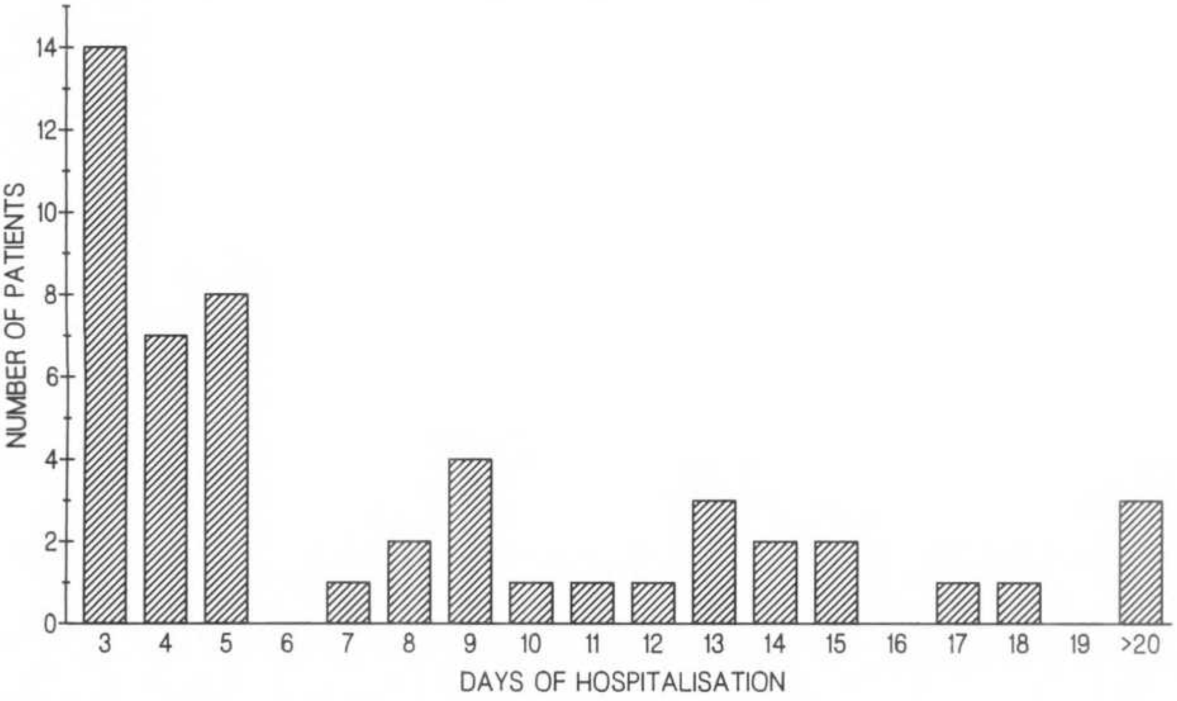

Fig. 3 Duration of hospitalisation for 49 patients undergoing elective orchiectomy.

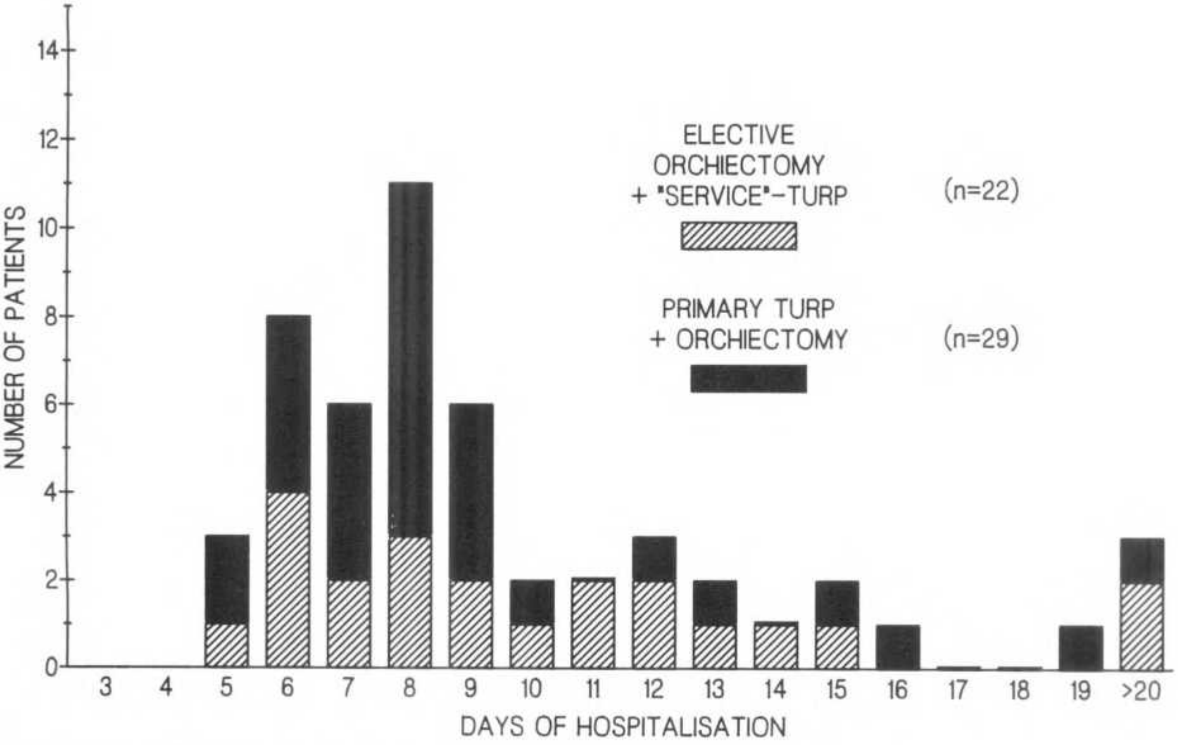

Fig. 4 Duration of hospitalisation for 51 patients undergoing orchiectomy plus TURP.

generally accepted. In very old and asymptomatic patients orchiectomy was not performed despite advanced disease. Although a few patients are less than 70 years old and only slightly disabled from their disease, prostatic cancer patients who are offered orchiectomy should be regarded as elderly, frail individuals with advanced malignant disease.

In the case of the 22 patients whose orchiectomy was combined with TURP, many urologists may argue that the latter procedure was probably unnecessary as one should have awaited the effects of orchiectomy. However, the decision to perform TURP was taken by experienced urologists well aware of the castration effect. Retrospectively, we consider that this operation did benefit the patient and it did not prolong the period of hospitalisation. For the 29 patients admitted primarily for surgery to the prostate, orchiectomy involved little extra cost (McClinton *et al.*, 1989). These patients left hospital earlier than those undergoing elective orchiectomy only, which probably indicates that this group of patients is less disabled by their prostatic cancer.

Since 11 of the 49 patients undergoing elective orchiectomy needed hospitalisation because of complications, it appears that approximately 60% of the orchiectomies in the present study were carried out in patients already hospitalised because of complications from their prostatic cancer. This indicates that estimation of the cost of orchiectomy as an isolated procedure based on an assumption of 2 days' hospitalisation (McClinton *et al.*, 1989) is irrelevant in most patients. Our period of hospitalisation are comparable to those reported by Carlsson *et al.* (1989).

Being a minor operation, orchiectomy is usually placed last on the day's operation list. This implies a risk of postponement if other emergency operations have to be performed. However, post-operative delay due to social problems and difficulties with residential accommodation was the main reason for prolonged hospitalisation. Obviously, this bears no relation to the surgical treatment but reflects general problems associated with the hospitalisation of elderly, frail patients, many of whom are in a difficult social situation before admission. Hospitalisation for orchiectomy and discharge to permanent residential accommodation often relieves the patients' families of heavy burdens. We fear that for many patients castration outside hospital would not have brought to light complications which were detected and treated during hospitalisation. The few complications seen after orchiectomy seem to promote the idea of orchiectomy as an out-patient procedure, as do social problems related to the hospitalisation of old, seriously ill men. However, the finding that 21% required peri-operative blood transfusion and 37% had some degree of renal failure indicates that closer observation is needed. An enquiry at the Congress of the Nordic Urological Association held in Reykjavik in July 1989 revealed that very few Nordic urologists practise orchiectomy on an out-patient basis.

It appears that orchiectomy during hospitalisation remains a cost-effective method of castration in most cases. One result of the introduction of medical castration is a more critical attitude towards the cost of treatment of prostatic cancer. According to figures from the Norwegian Cancer Registry, the expected survival time for a 76.4-year-old patient with advanced prostatic cancer is 2.5 years. This means 36 monthly injections of depot preparations of LH–RH analogues currently available. Patients who are being offered castration for carcinoma of the prostate constitute a heterogenous group. Some might undergo orchiectomy as out-patients while others should avoid surgery and receive medical castration. The best choice depends on individual evaluation of each patient by a responsible urologist.

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High-dose Medroxyprogesterone Acetate versus Estramustine in Therapy-resistant Prostatic Cancer: A Randomised Study

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Summary—A series of 105 patients with metastatic prostatic cancer, having progressed on first-line hormonal treatment, were randomised to high-dose medroxyprogesterone acetate (MPA) 1000 mg i.m. daily for 15 days, followed by 1000 mg weekly (53 patients), or to estramustine 280 mg *per os* twice daily (52 patients). The treatment was discontinued because of side effects in 3 of 51 evaluable MPA-treated patients and in 8 of 51 evaluable estramustine-treated patients. Progression-free survival was short in both groups and no statistically significant difference between them was observed. After 1 year, 70% of the patients had died and there was no statistically significant difference between the 2 treatments in the cumulative observed survival rates. According to modified SPCG criteria, remissions lasting from 12 to 56 weeks were noted in 13 MPA-treated patients and in 4 estramustine-treated patients. This difference was statistically significant. After cross-over, 6 of 33 patients in the MPA group had a remission compared with 1 of 24 in the estramustine group. It was concluded that the response rate, considering both subjective and objective response criteria, was better with MPA and the side effects were fewer.

Although many clinical studies have been carried out, the role of non-hormonal cytotoxic therapy in the management of patients with prostatic cancer has yet to be established. A review of several prospective randomised clinical trials has shown that none of the chemotherapy programmes produced a better survival rate than that found in the control groups (Eisenberger *et al.*, 1985). Estramustine is a widely used chemotherapeutic agent and has shown response rates in up to 30% of hormone-resistant patients (Jönsson *et al.*, 1977; Edsmyr *et al.*, 1980; Nilsson 1980). In the Nordic countries, estramustine has been the first standard treatment in therapy-resistant cases.

Previous reports have shown the beneficial effect of high doses of medroxyprogesterone acetate in such patients (Bouffioux, 1976; Nilsson, 1982; Fosså *et al.*, 1985). In patients with prostatic cancer who have progressed on first-line hormonal treatment, the theoretical action of MPA consists of increased catabolisation of circulating androgens (Bardin and Catterall, 1981), cortisol-like activity (Denis and Bouffioux, 1983) and/or a direct weak cellular effect, such as direct binding of progesterone to cellular androgen receptors (Attramadal *et al.*, 1977). However, the mechanism of pain relief by means of high-dose MPA may be very complicated (Sasagawa and Satomi, 1990).

In a pilot study, we gave high doses of medroxyprogesterone to 20 patients with therapy-resistant prostatic cancer and 4 of them showed a partial response for periods of up to 24 months (Johansson and Lingårdh, 1985). We therefore undertook this randomised study to compare MPA with estramustine in terms of safety, palliation and survival in patients with metastatic prostatic cancer who had progressed on first-line hormonal treatment.

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Patients and Methods

In this hospital, which has a catchment area of about 195,000 inhabitants, approximately 100 new cases of prostatic cancer are diagnosed each year. Since 1977, therapy and follow-up have been standardised. In advanced stages the patients have been treated initially with oestrogen, the antiandrogen flutamide or orchiectomy (Johansson *et al.*, 1987, 1990). The TNM and WHO classifications have been used (UICC, 1978; International Histological Classification of Tumours, 1980). In newly diagnosed patients with prostatic cancer 25% have metastases (M1), 40 to 45% are localised and the remainder have locally advanced cancer without metastases (T3–4, NX, MO).

From March 1983 onwards, all patients with progressive metastatic prostatic cancer who had been treated according to the routine protocol were considered for randomisation to either MPA (Farlutal Depot®) 1000 mg i.m. daily for 15 days followed by 1000 mg i.m. weekly, or to estramustine (Estracyt®) 280 mg *per os* twice daily. Only patients without serious cardiovascular disease who had not been treated with chemotherapy, estramustine or progesterone compounds were included.

After the start of this second-line treatment the patients were followed up by means of clinical examination, laboratory tests (acid phosphatase, alkaline phosphatase, haemoglobin, creatinine and sedimentation rate) and bone scan at least every 3 months. Their response to therapy was assessed for the first time after 6 to 12 weeks. Almost all clinical check-ups were performed by 2 urologists (J.E.J. and S.O.A.).

The principal aim of the study was to compare the 2 arms of treatment to which the patients were initially randomised. After progression, however, the patients were crossed over to the other treatment wherever possible.

Definition of end-points

According to the protocol, response to treatment was to be determined in accordance with the criteria drafted by the Scandinavian Prostatic Cancer Group (SPCG). However, it soon became evident that these criteria had to be modified slightly in patients with therapy-resistant prostatic cancer in whom skeletal pain and a lowered performance status were the main problems. The modifications proposed by Fosså *et al.* (1985) were therefore used in all patients when treatment was evaluated (Table 1). Progression was defined as an increase of 25% of more in the volume of the measurable lesions, a significant increase in the extent of existing lesions as seen on bone scan or the occurrence of any new lesion. An increase in acid phosphatase values alone was not considered to indicate progression. Progression-free survival was defined as the time until progression recurred or death caused by prostatic cancer (if not preceded by progression).

Statistics

Progression-free survival and observed survival with regard to all causes of death were estimated by the Kaplan-Meier method. To test the equality of survival curves for the 2 treatment groups the log-rank test was used. The response rates and the proportion of patients with side effects were compared by a standard chi-squared test.

In 105 patients the study had a 55% power to detect a response rate of 50% in the estramustine-treated arm, assuming that MPA treatment yields a 30% response rate and that a 2-sided test on the 5% level of statistical significance was performed.

Table 1 Response criteria according to SPCG

	Progression	*No change*	*Remission*
Primary tumour	> 25% volume increase	≤ 25% volume increase	> 50% volume reduction
	and/or	and/or	and/or
Metastases	> 25% volume increase	≤ 25% volume increase or ≤ 50% reduction	> 50% volume reduction
	or	and (or)*	and (or)
Acid phosphatase	> 50% increase	unchanged	normalisation
	or	and (or)	and (or)
Performance status	worsened	unchanged	normalised or improved by ≥ 2 steps (Karnofsky)

*( ) indicates modifications for patients with hormone-resistant prostatic cancer (Fosså *et al.*, 1985)

Results

Between March 1983 and January 1989, 53 patients were randomised to the MPA group and 52 to the estramustine group. Two were lost to follow-up. One patient was subsequently judged to be ineligible since there was no objective evidence of metastases. One patient was treated with oral MPA instead of injections and was considered to belong to his randomisation arm. Thus 51 MPA-treated and 51 estramustine-treated patients were evaluated. The patients' characteristics are shown in Table 2. The distribution of patients according to particular prognostic factors was similar, but more patients had pain in the MPA group. The concentration of testosterone in serum was measured in 20 patients in each group. All of those in the estramustine group had a "castration level" (<2 nMol/l). In the MPA group 2 patients had slightly elevated levels (2.9 and 6.7).

Table 2 Details of 102 Patients Randomised to Treatment with MPA or Estramustine

	MPA (n=51)	*Estramustine (n=51)*
Mean age (years) (range)	73 (58–85)	74 (61–85)
Mean time from diagnosis to trial start (months)	39 (3–142)	41 (4–131)
Previous treatment		
Orchiectomy	39	39
Oestrogens	7	6
Flutamide	5	6
T category		
T0–2	1	6
T3–4	50	45
M1 category		
Skeletal	49	50
Lymph nodes	2	—
Pleural	—	1
Histological grade		
I	1	4
II	28	19
III	22	28
Acid phosphatase increased	33	37
Pain	42	35

Side effects

The frequency of side effects is shown in Table 3. Four patients in the estramustine group and 8 in the MPA group developed oedema or cardiovascular complications. Ten patients receiving estramustine developed gastrointestinal side effects (nausea, vomiting and/or diarrhoea) and in 5 cases the treatment had to be discontinued. Three patients felt a substantial increase in pain after commencing treatment with MPA. Therapy was discontinued in 8 patients in the estramustine group because of side effects and in 3 cases in the MPA group.

Table 3 Side Effects (Numbers of patients who had to discontinue treatment are shown in parenthesis)

	MPA (n=51)	*Estramustine (n=51)*
After randomisation		
Oedema	4 (2)	2 (2)
Cardiovascular	4 (1)	2 (1)
Gastrointestinal	–	10 (5)
Pain	3	–
Total	11 (3)	14 (8)

$\chi^2_{1df}=0.21, P=0.64$
$(\chi^2_{1df}=1.63, P=0.20)$

	MPA (n=33)	*Estramustine (n=24)*
During cross-over		
Oedema	7	5 (2)
Cardiovascular	1	1
Total	8	6 (2)

$\chi^2_{1df}=0.06, P=0.81$
$(\chi^2_{1df}=0.92, P=0.34)$

Progression-free survival

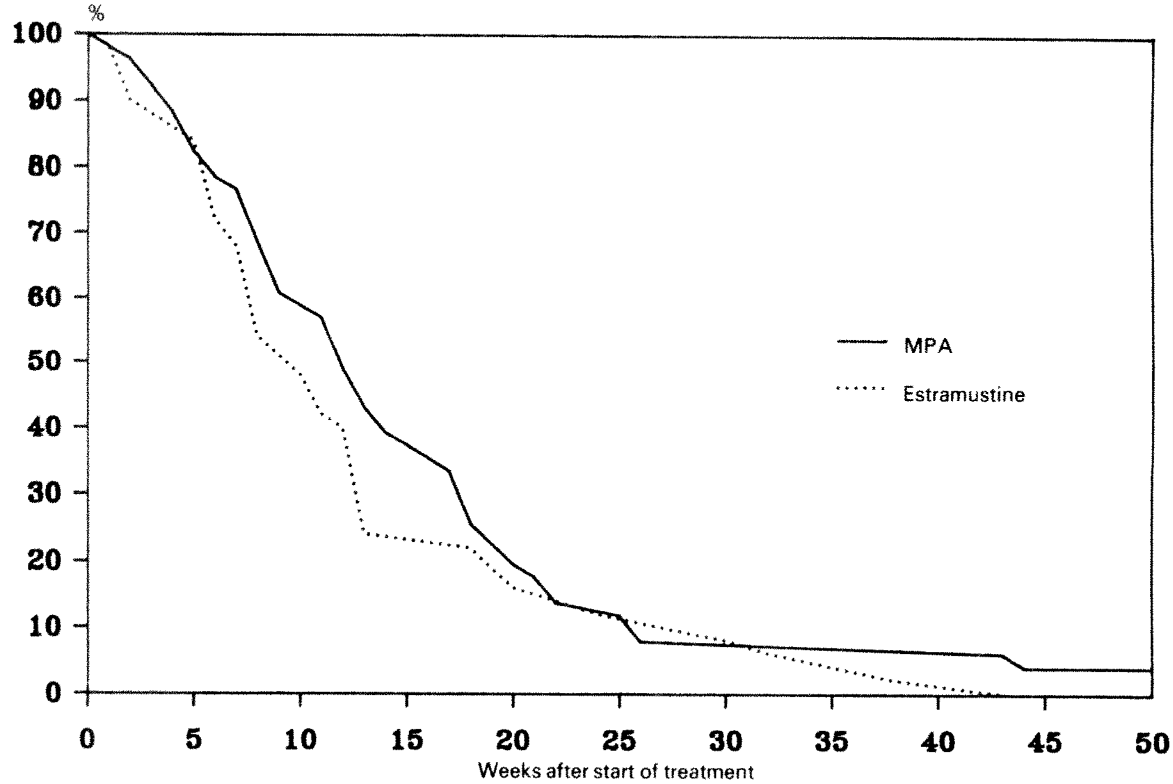
Progression-free survival was short: after 3 months the disease had progressed in more than half of the patients (Fig. 1). There was no statistically significant difference between the 2 groups in the log-rank test ($P=0.28$).

Survival

During the first year of treatment 70% of the patients died. The cumulative survival curves showed a slight tendency to improve during the first 50 weeks in patients initially treated with estramustine but there was no statistically significant difference between the 2 groups in the log-rank test ($P=0.23$) (Fig. 2).

Response

According to modified SPCG criteria for response, 13 MPA-treated patients (25%) had remissions lasting 12 to 56 weeks compared with 4 (8%) in the estramustine group, whose remissions lasted from



$\chi^2 = 1.16$ ($P = 0.281$)

Fig. 1 Cumulative proportion of patients without progression of disease initially randomised to treatment with MPA or estramustine.

22 to 28 weeks (Table 4). This difference was statistically significant ($P = 0.034$). No change was seen in 7 and 16 patients respectively in these 2 groups. There was also a statistically significant difference between the combination of patients in remission and no change in the 2 treatment groups ($P = 0.05$).

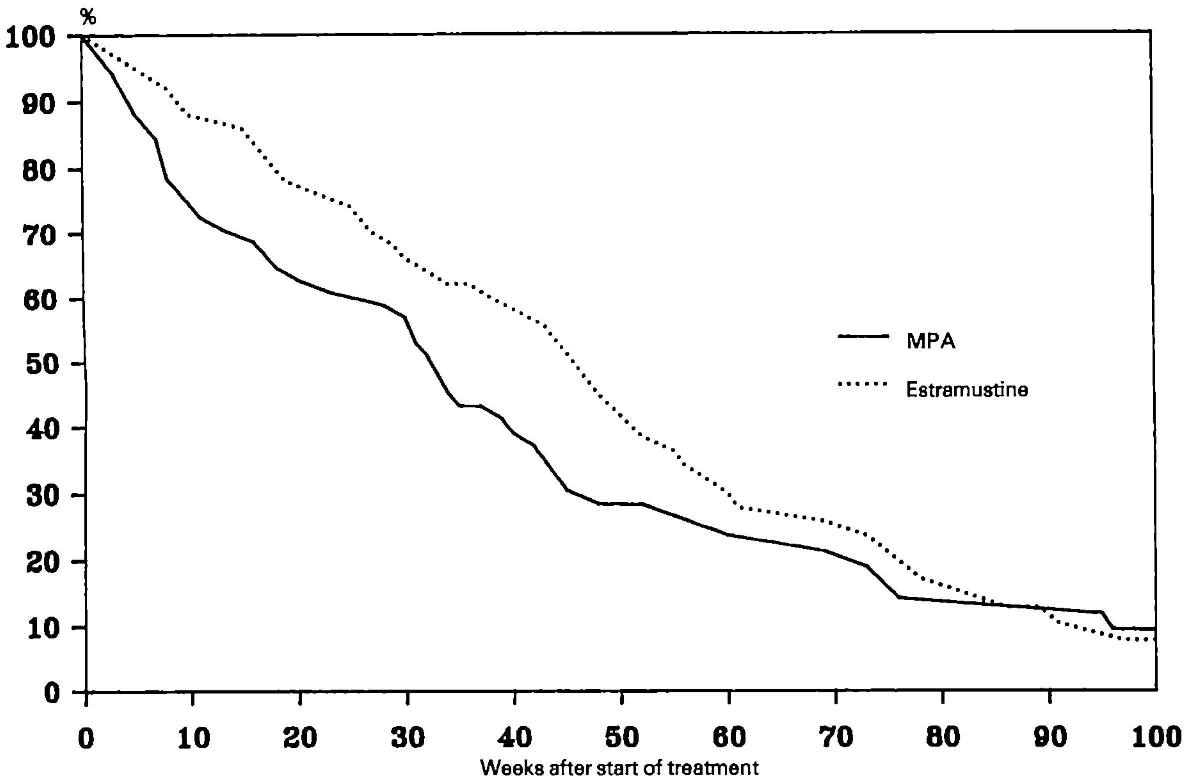
Of the 13 patients with remission in the MPA group, 12 had undergone orchiectomy and 1 had been treated with oestrogen. Four of these 13 patients had a significant decrease in the extent of existing lesions on the bone scan. All others with skeletal metastases had no change after a period of increased activity before inclusion in the study. Two had a decrease of 50% or more in the volume of the primary tumour and 2 had the same decrease in lymph node metastases. Acid phosphatase values became normal in 6 patients and reduced by 50% or more in 3 patients. The remaining 4 patients had unchanged normal values. In the estramustine group 1 patient had undergone orchiectomy, 1 had been treated with oestrogen and 2 with flutamide. Two of these 4 patients with remission showed a significant reduction in activity on the bone scan and the remainder had no change. Acid phosphatase values became normal in 2 patients and reduced by 50% or more in the other 2 patients.

Cross-over

Following progression of disease or discontinuation of treatment because of side effects, 24 patients in the MPA group were crossed over to estramustine. Six of these suffered side effects and 1 had a remission lasting 16 weeks. Of 33 patients who were crossed over from estramustine to MPA, 8 developed side effects and 6 had remissions lasting 12 to 96 weeks (Tables 3 and 4).

Discussion

This study has shown that the prognosis after progression of disease following first-line hormonal treatment in patients with prostatic cancer was



$\chi^2 = 1.42$ ($P = 0.233$)

Fig. 2 Cumulative observed survival in patients initially randomised to treatment with MPA or estramustine.

bad, with a mortality of 70% within 1 year. There was no statistically significant difference between patients randomised to treatment with high-dose MPA or estramustine in the progression-free or observed survival. More patients randomised to MPA (13 versus 4) had a response according to modified SPCG response criteria, which entails an improvement in performance status in combination with normalisation or at least a 50% reduction in acid phosphatase or regression of the primary tumour or of the metastases, but not up to 50%. This may indicate a more favourable subjective response and fewer of the tumour-related symptoms that are most important for the quality of life in this category of patients, if other effects of treatment cannot be achieved. No patient with remission or no change had skeletal pain requiring the use of analgesics. Ten estamustine-treated patients developed gastrointestinal side effects; 3 patients in the MPA group experienced increased pain during the first 2 weeks of treatment.

The study was population-based and performed in a single hospital, the follow-up procedures were standardised and remained unchanged for the whole study period. Most of the check-ups were carried out by 2 urologists. There was no evidence of a selection bias and all patients with progressive prostatic cancer were included. Studies comprising only patients who have measurable metastases may have a selection bias as they may include patients with comparatively good prognoses.

It is difficult to find adequate response criteria for patients who have progressed on first-line hormonal treatment (Schmidt *et al.*, 1976; Paulson *et al.*, 1979). The criteria used by the National Prostatic Cancer Group (Murphy and Slack, 1980), those used by the EORTC (Schröder, 1980) and those from the Scandinavian Prostatic Cancer Group (SPCG) (Fosså *et al.*, 1985) are not suitable for evaluating the response in hormone-resistant cases. We have therefore used the modified SPCG response criteria proposed by Fosså *et al.* (1985). The skeletal activity of the metastases on the bone scan is difficult to interpet: patients with remission in this study had either an unchanged or a significant reduction of activity. In an earlier evaluation these

Table 4 Response to Treatment with MPA and Estramustine after Randomisation and to Cross-over Treatment according to Modified SPCG Criteria

	MPA	*Estramustine*
After randomisation		
No. of patients	51	51
Remission	13	4
Duration in weeks	12–56 ($\chi=27$)	22–38 ($\chi=29$)
No change	7	6
Duration in weeks	12–26 ($\chi=18$)	20–43 ($\chi=28$)
Progression	29	34
Treatment discontinued	3	8

Remission: $\chi^2_{1\,\mathrm{df}}=4.51$, $P=0.034$
Remission + no change: $\chi^2_{1\,\mathrm{df}}=3.83$, $P=0.05$

	MPA	*Estramustine*
After cross-over		
No. of patients	33	24
Remission	6	1
Duration in weeks	12–96 ($\chi=36$)	16
No change	6	3
Duration in weeks	10–43 ($\chi=23$)	21–27 ($\chi=25$)

Remission: $\chi^2_{1\,\mathrm{df}}=1.4$, $P=0.24$
Remission + no change: $\chi^2_{1\,\mathrm{df}}=1.78$, $P=0.18$

criteria correlated well with the clinical course (Johansson *et al.*, 1980).

MPA as a single drug has relieved symptoms in patients with therapy-resistant disease (Bouffioux, 1976; Pavone-Maculuso *et al.*, 1978). A high dose tends to produce better results (Nilsson, 1982; Johansson and Lingårdh, 1985). In a randomised study from Norway (Fosså *et al.*, 1985), MPA (1000 mg orally/day) induced a remission in 8 of 21 patients, whereas prednisolone (20 mg orally/day) induced a remission in 3 of 24 patients. The response criteria were the same as those used in the present study and no survival benefit for either drug was observed. Two other studies from the Nordic countries have shown better subjective response rates with a combination of MPA and farmorubicin than with estramustine (Tveter, personal communication; Anderström, personal communication).

As a single therapy in hormone-resistant cases, response rates for estramustine have been reported in up to 30% (Eisenberger *et al.*, 1985; Jönsson *et al.*, 1977; Edsmyr *et al.*, 1980). However, different criteria for response were used in these studies and factors influencing the selection of patients may have affected the outcome. There is no other published randomised study that compares estramustine with MPA as a single drug.

Because of the size of the study and the ability to detect differences in response to therapy, clinically important survival differences may not have been detected in this study. However, a review of several studies (Eisenberger *et al.*, 1985) showed no survival advantage for estramustine treatment and in our analysis the survival curves crossed after 90 weeks of follow-up. If there exists a survival advantage for estramustine, it is probably small and of little clinical relevance considering the many side effects. Palliation and quality of life are very important and patients with fewer tumour-related symptoms will probably have better overall palliation. The response rate must be weighed together with the side effects.

In conclusion, we found no benefit in progression-free or observed survival when comparing MPA and estramustine in therapy-resistant patients. However, when considering both subjective and objective response criteria, the response was better with MPA and serious side effects were fewer. Thus MPA is preferable to estramustine in the treatment of this category of patients. Palliation is usually short-lived and if no subjective effect is achieved after 2 months, the treatment can be changed.

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Morphometric Evidence for Bone Resorption and Replacement in Prostate Cancer

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Summary—A series of 78 patients with metastatic bone disease from prostate cancer underwent iliac crest biopsy, enabling histomorphometric quantification of eroded bone surface and bone volume in both tumour-free and metastatic bone tissue. Eroded surfaces in tumour-free specimens were high in patients with active compared to stable disease but bone volume was maintained in both groups, whilst in bone surrounding micrometastases ($n = 8$) eroded surfaces were further increased and bone volume reduced. Eroded surfaces within metastases were greater still but were associated with increased bone volume due to replacement of the existing trabecular tissue with abnormal woven bone, giving an overall appearance of sclerosis. These results show that the effect of prostate cancer on bone tissue is complex, involving differential disturbance of bone formation and resorption within metastases, in bone surrounding tumour invasion and in the tumour-free skeleton.

The osteoblastic nature of bone metastases in patients with prostate cancer has long been established (Milch and Changus, 1956). However, the concept that synchronous bone resorption might occur in the presence of accelerated bone formation is much more recent (Galasko, 1976; Urwin *et al.*, 1985).

Biochemical measurement of the fasting urinary excretion of hydroxyproline has shown significant increases in levels of this marker in patients with metastatic bone disease from prostate cancer (Percival *et al.*, 1987), suggesting that the extent of bone destruction associated with this condition may be considerable.

Histological changes consistent with increased bone resorption have been reported within bony metastases of patients dying from prostate cancer (Galasko, 1976) and histomorphometric analysis of metastatic bone tissue from patients with this condition has confirmed abnormally high resorptive indices (Valentin-Opran *et al.*, 1980; Charhon *et al.*, 1983; Bürki *et al.*, 1987). Further studies have also suggested that resorption is high not only within metastases but also within tumour-free bone distant to neoplastic infiltration (a phenomenon thought to arise from increased skeletal mobilisation of calcium (Percival, 1986)) to the extent that bone resorption is greater in the tumour-free skeleton than it is within tumour deposits (Urwin *et al.*, 1985; Percival *et al.*, 1987).

To clarify the extent of bone resorption and the changes in bone volume in relation to disease activity and tumour invasion this study has used standardised histomorphometric techniques to measure these parameters in bone tissue from the tumour-free skeleton, from areas surrounding metastatic foci and from areas of complete tumour infiltration of the marrow space in a group of patients with metastatic bone disease from prostate cancer.

Patients and Methods

The study group comprised 78 patients with histologically proven prostate cancer and scintigraphic evidence of metastatic bone disease. Patients were either untreated or had undergone

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hormone manipulation by orchiectomy or luteinising hormone releasing hormone analogue therapy at least 6 months prior to bone biopsy. No patients were taking oestrogens before the study; transiliac trephine core biopsies 8 mm in diameter were taken from a standard site 2.5 cm below and behind the anterior superior iliac spine in all patients using a modified Bordier drill (Lalor *et al.*, 1986). Specimens were alcohol fixed and resin embedded prior to undecalcified section and staining. Sections were examined microscopically for the presence of tumour and classified as tumour-free or infiltrated.

Tumour-free biopsies were further sub-classified according to the patients' disease activity at the time of biopsy. All patients prior to hormone manipulation (unmanipulated) (UM) (n = 23) had scintigraphic evidence of advancing disease. Patients who had undergone hormone manipulation (all at least 6/12 previously) were classified as manipulated stable (MS) (n = 13) or manipulated active (MA) (n = 13) on the basis of consecutive scintigraphic changes over 6 months prior to biopsy.

Tumour-infiltrated biopsies were further subdivided into those with a microfocus of tumour (MF: <50% of the marrow space affected by tumour) (n = 8) and those with total tumour infiltration (TT: tumour infiltration throughout the marrow space) (n = 21). All patients in the tumour subgroups had active disease according to bone scan and tumour markers.

Undecalcified microscopic sections from each specimen were stained using the von Kossa silver method (Pearse, 1985) before histomorphometric quantification. This was achieved by means of line intersect counting techniques using a Merz eyepiece graticule (Merz and Schenk, 1970). In this way the extent of the bone surface undergoing erosion was measured and expressed as a percentage of the total bone surface. Measured areas of erosion included resorption cavities containing osteoclasts (active resorption surface) and cavities with no osteoclasts (inactive resorption surface). Values for these 2 areas were summated and expressed as the Eroded Surface in accordance with standardised nomenclature (Parfitt *et al.*, 1987). This is a direct measure of the degree of bone destruction.

Bone volume was measured by microscopic point counting methods using a Merz graticule. Overall bone volume (the total volume of mineralised and unmineralised bone tissue) was initially determined

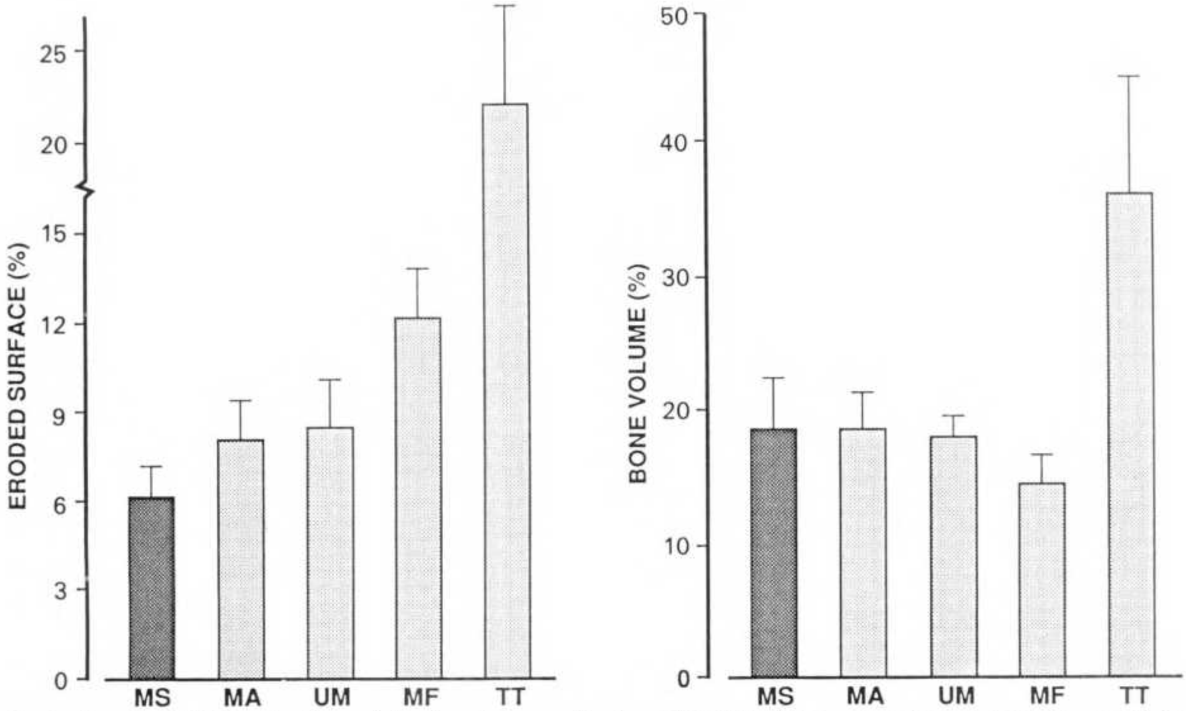

Fig. 1 Mean (±95% CL) values for eroded surface. In tumour-free bone (MS, MA, UM), erosion is increased with disease activity ($P<0.001$). Tumour encroachment (MF) increases resorption still further (UM vs MF) ($P<0.001$) whilst destruction is greatest within metastases (TT vs MF) ($P<0.0001$).

on von Kossa stained undecalcified sections. Differential measurements of lamellar bone (bone derived from the pre-existing skeletal tissue) and woven bone (bone laid down in response to malignant infiltration) were then measured on undecalcified, unstained microscopic sections viewed in light transmitted through crossed, polarising filters (a technique which enables easy differentiation of lamellar from woven bone). Surface and volume measurements were taken throughout the cancellous bone in Unmanipulated, Manipulated Stable, Manipulated Active and Total Tumour specimens whilst in Microfocus biopsies analysis was undertaken only in the tumour-free cancellous areas away from the region of tumour infiltration.

Measured histomorphometric values in tumour-free bone were compared statistically by analysis of variance. Comparison of eroded surface in total tumour specimens with tumour-free and of lamellar bone volume with tumour-free bone volume was by the Kruskall-Wallis test for non-parametric data.

Results

Analysis of tumour-free bone showed that eroded surface was lower in patients with stable (MS patients) than in those with active disease (UM and MA patients) (mean $\pm 95\%$ CL, $\mathrm{MS}=6\pm1.2$: $\mathrm{UM}=7.9\pm1.2$ ($P<0.001$), $\mathrm{MS}=6\pm1.2$: $\mathrm{MA}=7.9\pm1.2$ ($P<0.001$)) (Fig. 1) but trabecular bone volume was not significantly different between groups.

Bone tissue adjacent to surrounding microscopic tumour infiltration (MF) exhibited increased eroded surface when compared with the highest levels in tumour-free bone ($\mathrm{UM}=7.9\pm1.2$: $\mathrm{MF}=11.9\pm1.2$ ($P<0.001$)) and this was accompanied by a decreased bone volume ($\mathrm{UM}=18\pm3.5$: $\mathrm{MF}=15.2\pm2.5$ ($P<0.05$)).

Eroded surface in bone totally infiltrated by tumour was considerably increased by comparison with all other groups (median $\pm$ range, $\mathrm{MF}=12\pm8.8-16.2$: $\mathrm{TT}=18.4\pm2.8-50.7$ ($P<0.0001$)). Both lamellar and woven bone surfaces were eroded but overall bone volume was massively increased ($\mathrm{MS}=18.8\pm3.9$: $\mathrm{TT}=37.7\pm8.7$ ($P<0.0001$)). Differential lamellar/woven bone analysis revealed decreased lamellar bone volume in TT specimens (lamellar bone volume median $\pm$ range, $\mathrm{MA}=17\pm16\text{–}19$: $\mathrm{TT}=12.5\pm9\text{–}15$ ($P<0.0001$)) with replacement of pre-existing lamellar bone by woven bone (Figs 2 and 3). The amount of woven bone in tumour-free areas was negligible in all biopsies.

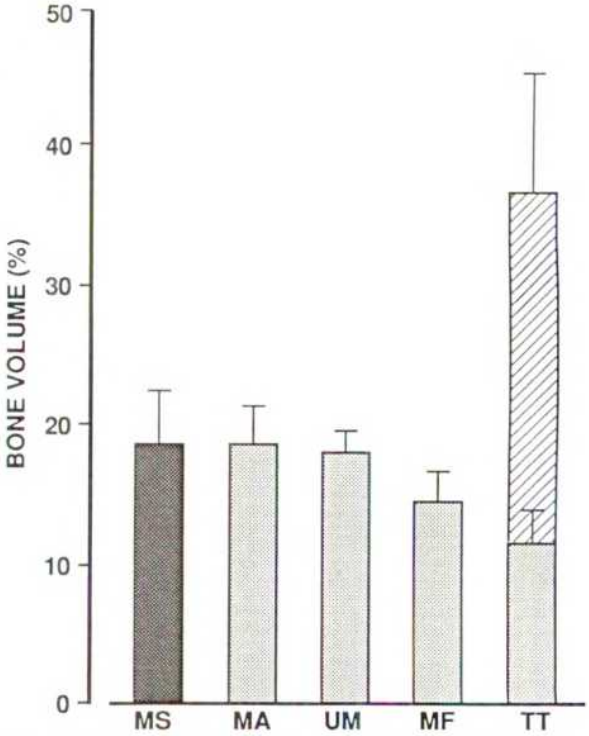

Fig. 2 Mean (+95% CL) values for bone volume showing decreases in areas surrounding neoplastic infiltration (UM vs MF) ($P<0.05$). Bone volume in TT biopsies increased overall due to woven bone deposition (hatched area) while the lamellar bone volume (stippled area) decreased still further compared to tumour-free ($P<0.001$).

Discussion

The results confirm that increased erosion in the tumour-free skeleton is implicitly linked with overall disease activity but the maintenance of bone volume despite accelerated destruction does suggest controlled homeostasis. The observed changes are likely to result from increased osteoclast activity due to elevations in circulating parathyroid hormone (PTH) and dihydroxy Vitamin D_3 (Charhon *et al.*, 1985; Urwin *et al.*, 1986), thought to be secondary to increased calcium requirement within metastases. However, it remains a possibility that as yet undiscovered circulating tumour-derived factors may have a role in this phenomenon, as has been described in other malignant conditions (Danks *et al.*, 1989; Heath *et al.*, 1990).

In specimens with a microfocus of tumour (Fig. 4) the increased resorption and decreased bone volume in excess of that seen in tumour-free biopsies

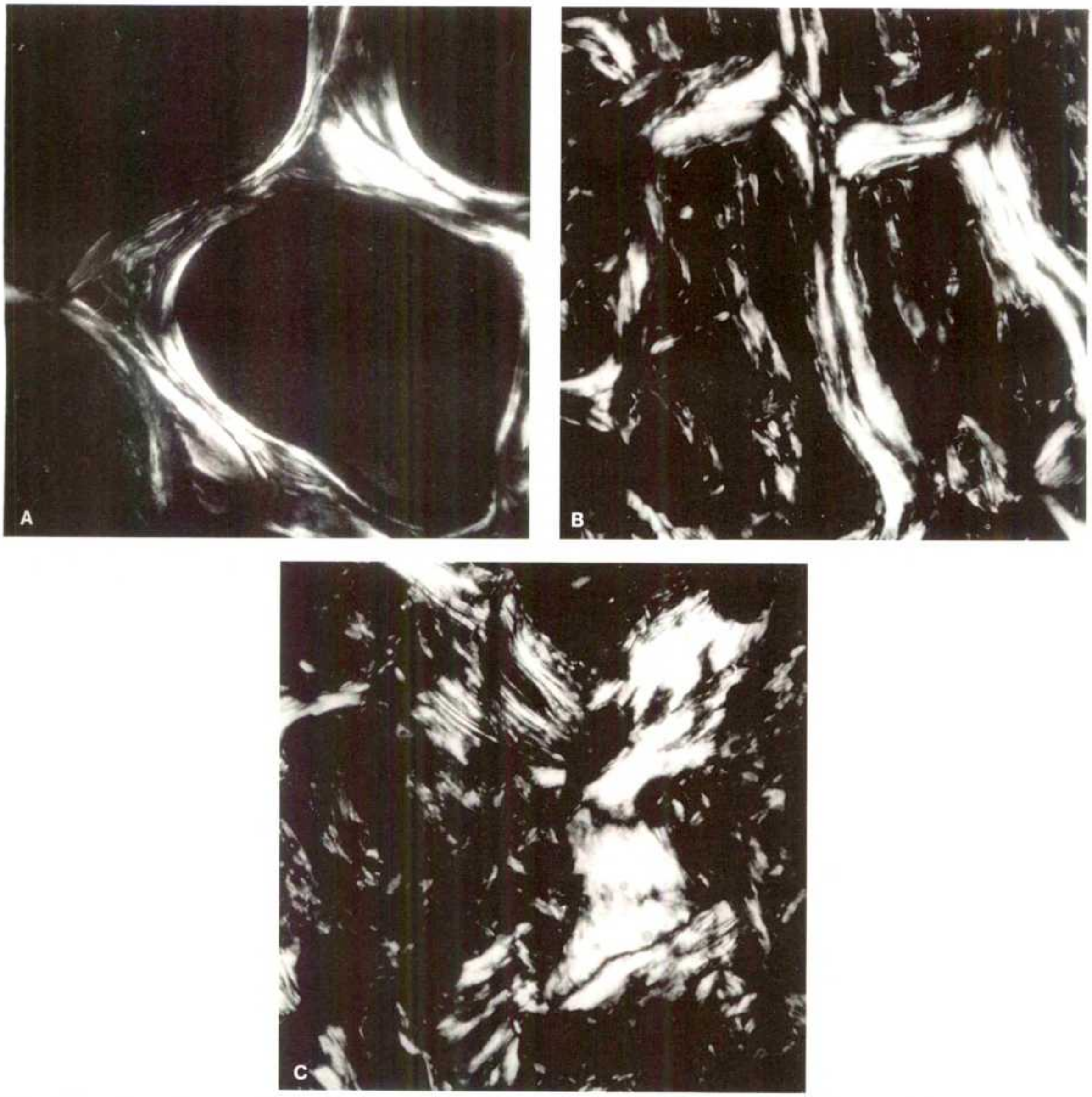

Fig. 3 Normal (A) and metastatic bone (B, C) under polarisation showing progressive lamellar bone destruction and woven bone replacement within metastases. (Crossed polarised light × 100).

confirms that tumour encroachment exerts a significant destructive effect on the bone surrounding areas of neoplastic infiltration. It is likely that this is due to the action of factors produced locally by tumour cells and released into the bone marrow space, thereby increasing osteoclast recruitment and osteoclastic bone resorption with resultant loss in bone volume. Since overall bone volume is a function of resorption and formation, the effect of tumour encroachment on osteoblast activity in the vicinity of metastases must also be taken into consideration. Any local activity inhibiting bone formation would potentiate the effect of osteoclastic resorption in lowering the bone volume.

Bone destruction in the presence of total tumour infiltration of the marrow space was usually

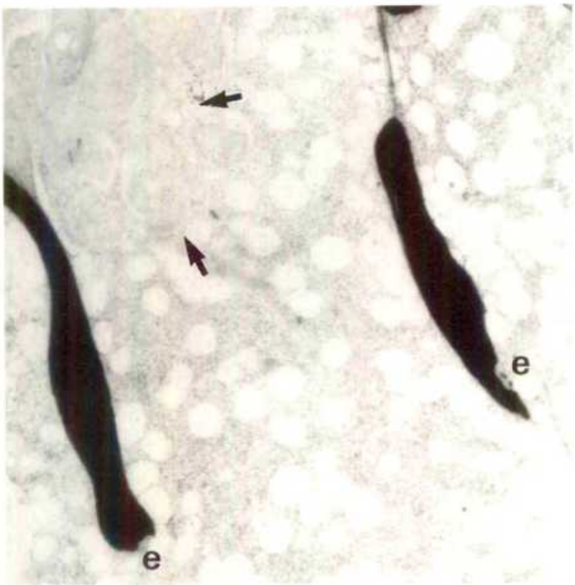

Fig. 4 Microfocus of prostatic carcinoma. Prostate cancer cells (arrowed) stimulate local osteoblast activity on the bone surface (top left). Areas of surface erosion (e) are seen on the surface of bony trabeculae in regions free of tumour. (Undecalcified bone; von Kossa and Cyanin × 66).

markedly increased, particularly in relation to levels seen in tumour-free or partially infiltrated areas, confirming the destructive local effect of neoplastic invasion. The increased surface erosion within metastases was consistent with that reported by other authors (Urwin *et al.*, 1985; Valentin-Opran *et al.*, 1980; Charhon *et al.*, 1983; Bürki *et al.*, 1987), although the degree observed in this study was greater in its extent. We would, however, disagree with the proposition that bone erosion is greater in tumour-free areas than in malignant deposits (Urwin *et al.*, 1985); our measurements demonstrate the reverse to be true.

The increased bone volume in the presence of biochemical and histomorphometric evidence of major bone resorption seems paradoxical but this is explained by the differential measurement of woven and lamellar bone volume. The analysis of bone sections in polarised light reveals evidence of major destruction within apparently sclerotic metastases in many patients (Figs 2 and 3). Woven bone produced by stimulated osteoblasts (Jacobs, 1983) is laid down on existing trabeculae and in the marrow space at a rapid rate and although woven surfaces are undergoing resorption at the same time as those in lamellar bone, the relative speed of bone formation results in increased overall bone volume while the pre-existing lamellar architecture by comparison continues to be eroded. In a number of specimens this was clearly demonstrated by almost complete destruction of the lamellar structures, which were synchronously replaced by abnormal woven bone (Figs 2 and 3). The overall effect produces the well recognised sclerosis associated with this disease. This degree of resorption and replacement is likely to account for the reported elevation in markers of bone tissue breakdown (Percival *et al.*, 1987) and it is probable that the contribution from the tumour-free skeleton is small by comparison.

The substances which stimulate intrametastatic bone destruction remain obscure. Malignant infiltration of bone is known to be associated with the production of substances which stimulate osteoclastic overactivity. One such substance is osteoclast activating factor (OAF), which has been shown to be produced by multiple myeloma (Mundy *et al.*, 1974). This has subsequently been shown to consist of the 3 separate substances, IL-1, TNF alpha 1 and TNF alpha 2 (Mundy, 1987), but prostate cancer cells have not yet been associated with these specific cytokines. Prostate cancer is, however, known to induce bone destruction. *In vitro* studies have shown that the prostate cancer cell line PC3 induces bone resorption (Rodan *et al.*, 1983) and animal studies have shown that early infiltration of bone by prostate cancer cells is associated with osteoclast mediated bone lysis (Pollard and Luckert, 1985; Nemoto *et al.*, 1988). Prostate cancer has also been associated with other cytokines which are known to promote bone resorptive activity. Human prostate cancer cells are known to possess mRNA for epidermal growth factor (EGF) (Morris and Dodd, 1990) and EGF and transforming growth factor alpha (TGF alpha) are produced by cultured prostate cancer cells (Connolly and Rose, 1990). Furthermore, the prostate cancer cell line PC3 is known to synthesise platelet-derived growth factor-like proteins (PDGF) (Sitaras *et al.*, 1988). EGF is known to promote osteoclast recruitment and differentiation (Vaes, 1988) and EGF, TGF alpha and PDGF will all stimulate osteoclasts to resorb bone (Raisz *et al.*, 1980; Tashjian *et al.*, 1982). It is possible that substances such as these are released by the tumour, thereby stimulating a secondary destructive mechanism mediated by osteoclasts.

In this study there were also a number of specimens in which extensive eroded bone surfaces were in direct contact with tumour, raising the possibility that destruction might have been, at least in part, due to the direct action of tumour cells; this observation has been made in previous reports (Milch and Changus, 1956; Galasko, 1976). The fact that some tumours have been shown to resorb bone directly *in vitro* (Eilon and Mundy, 1978) and that tumours are known to produce substances which directly break down the unmineralised skeleton (Woolley, 1984) lends further weight to the view that the bone destruction within metastases from prostatic carcinoma may be mediated not only by activation of local cellular mechanisms but also by the direct action of the tumour itself.

It is concluded that metastatic prostate cancer, a disease traditionally associated with bone formation and sclerosis, is responsible for substantial bone lysis affecting both the tumour-free and the metastatic skeleton. Resorption in tumour-free areas is increased but this has no effect on bone volume, whilst destruction surrounding regions of neoplastic infiltration is of greater magnitude, inducing a bone volume fall. Within metastases osteolysis is greater still, producing significant lamellar and woven bone destruction an effect which is obscured by the simultaneous, rapid deposition of new woven bone.

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Neurophysiology of the Striated Urethral Sphincter in Multiple Sclerosis

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Summary—Urethrovesical dysfunction is common in patients with multiple sclerosis. We present the results of urodynamic and neurophysiological studies in a series of 24 patients with multiple sclerosis associated with urinary symptoms. Urethral sphincter electromyography showed only minor abnormalities but studies of central conduction demonstrated abnormal sensory conduction in 88% and abnormal motor conduction in 80% of the patients studied. These abnormalities of central conduction correlated well with the urodynamic findings.

The most striking pathological feature of multiple sclerosis (MS) is the demyelination, which can affect any part of the central nervous system. McDonald (1974), after reviewing clinical and experimental evidence concerning the pathophysiology of multiple sclerosis, concluded: "It is clear that alterations in the passive cable properties of nerve fibres as a result of myelin loss lead directly to slowing of conduction and intermittent conduction block, or to complete conduction block (depending on the severity of the demyelination) and that all these defects contribute to the clinical deficit". The clinical deficit produced may be extremely variable because of the disseminated nature of the pathological changes and, in addition to abnormalities of locomotion, sensation and vision, urinary symptoms are common.

Bladder dysfunction may be the presenting symptom in 2% of patients and may develop during the course of the disease in up to 78% (Miller *et al.*, 1965). Typically, patients suffer from urinary incontinence, although retentive symptoms are common. Bradley *et al.* (1973), using rapid fill gas cystometry with synchronous anal plug electromyography (EMG), found that there were 2 main types of bladder dysfunction in MS, namely detrusor hyper-reflexia and detrusor areflexia. They also described an abnormality of sphincteric function which was present in a proportion of the patients. There was an involuntary increase in sphincteric EMG activity associated with the detrusor contraction which has become known as detrusor sphincter dyssynergia (DSD) (Blaivas *et al.*, 1981). Subsequent urodynamic studies have confirmed these findings, with hyper-reflexia (with or without DSD) present in the majority of patients and areflexia present in a variable minority (Blaivas *et al.*, 1979; Philp *et al.*, 1981; Petersen and Pedersen, 1984). It has been suggested that these urodynamic abnormalities result from lesions within the cervical cord (Philp *et al.*, 1981) and indeed it has been shown in pathological studies that the cervical region is the commonest site of spinal cord involvement in multiple sclerosis (Oppenheimer, 1978).

Several studies have attempted to correlate clinical signs and urodynamic abnormalities in patients with a neurogenic bladder due to multiple sclerosis. Goldstein *et al.* (1982) found a positive correlation between the presence of detrusor hyper-reflexia and deep tendon hyper-reflexia, while Awad *et al.* (1984) found a positive correlation between detrusor hyper-reflexia and both corticospinal and cerebellar signs in the legs.

Clinical neurophysiological testing provides a means of objectively measuring neuronal conduction and the aim of this study was to correlate the

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urodynamic and neurophysiological findings in a group of patients with multiple sclerosis associated with urinary symptoms.

Patients and Methods

A group of 24 patients with urinary symptoms and multiple sclerosis was studied. There were 9 men and 15 women with a median age of 40.5 years (range 20–62). Details of the patients and the degree of disability (Kurtzke, 1970) are shown in Table 1. Low Kurtzke scores are associated with mild disability; for instance, patients with Kurtzke grade 1 have no clinical disability and only mild clinical signs, while patients with Kurzke grade 5 can walk a maximum of only 200 yards unaided and those with grade 9 disability are bedridden, although they can communicate and eat. The patients in this study tended to be those who had mild overall disability and those who would best tolerate the wide range of investigations in this study.

All patients underwent a series of neurophysiological investigations and urodynamics as described below and the results were compared with those found in 13 control subjects with no evidence of urethrovesical dysfunction or neurological disease. There were 9 men and 4 women with a median age of 52 years (range 22–76). All controls underwent EMG studies and urodynamics, 12/13 underwent sacral reflex studies, and 11/13 underwent assessment of central sensory and motor pathways.

Table 1 Details of Patients

Patient	*Sex*	*Age (years)*	*Duration of disease (years)*	*Kurtzke grade*	*Urinary symptoms*
M.G.	F	39	8	2	Urgency
C L	F	33	4	3	Urge incontinence
N.A.	M	48	25	6	Urge incontinence
A.R.	F	40	15	7	Urge incontinence
I.B.	F	47	2	2	Urgency
K.G.	F	52	22	7	Urge incontinence
A.B.	F	27	4	6	Hesitancy/ retention
D.S.	F	44	27	4	Hesitancy/urgency
J.L.	F	43	3	3	Hesitancy/urgency
R.S	M	37	4	3	Urge incontinence
R.A.	M	33	2	2	Urgency
F.W.	F	59	26	3	Urge incontinence
M F	M	41	13	3	Urge incontinence
J.D	F	62	17	6	Urgency
E.M.	F	58	14	3	Urge incontinence
V C	F	35	16	5	Retention
L.E.	M	39	13	4	Urge incontinence
E.D.	M	30	5	5	Urge incontinence
A.D.	F	37	12	5	Urgency
R W.	M	41	8	3	Hesitancy/urgency
D.L.	M	49	7	3	Urgency
J.S.	F	46	6	5	Urgency
L W.	F	20	6	6	Hesitancy/urgency
C.L.	M	33	6	5	Hesitancy

A. Neurophysiological Studies

In all neurophysiological studies the patient was earthed via a saline soaked electrode attached to the thigh.

1. *Urethral sphincter EMG with motor unit analysis*

Male patients lay in the left lateral position with flexed hips during insertion of the needle electrode while women were asked to lie in a supine position with the hips flexed and abducted. A concentric needle electrode was then inserted in the following way. In men, the index finger of the investigator's left hand was inserted into the rectum. The electrode was then introduced through the perineum in the midline to the level of the apex of the prostate. In women, the needle was inserted approximately 1 cm lateral to the external urethral meatus and guided anteriorly towards the midline. Positioning of the needle within the striated urethral sphincter was aided by listening for the characteristic tonic activity of the striated sphincter on the audio output of the electrophysiological recording unit.

Individual motor units were identified using a delay line and signal triggering as described by Fowler *et al.* (1984); 5 to 10 motor units were analysed and their duration, amplitude and polyphasicity assessed. The mean motor unit duration and amplitude was calculated for each patient and in addition the total number of polyphasic motor units was noted.

2. *Sacral reflex latency*

With the concentric needle electrode *in situ*, the sacral reflex latency was then measured. The stimulus was provided by 2 saline soaked electrodes, 2 cm apart. They were applied to the dorsum of the base of the penis or clitoris in the midline, with the anode most proximal. Square-wave stimuli of duration 0.1 ms were applied at a frequency of 1 Hz and the stimulus intensity was gradually increased from zero, up to the threshold of sensation, which was recorded. The stimulus was then further increased until a response was recorded in the urethral sphincter or until the stimulus became too strong for the patient to tolerate. Confirmation of the presence of the response was aided by palpation of the bulbocavernosus reflex in men, and by hearing the EMG response on the audio output of the electrophysiological recorder. The intensity of the stimulus which regularly provoked an EMG response was recorded (usually 2–3 times the sensory threshold).

Using a signal trigger, 10 responses were recorded and the shortest latency of the EMG response was then measured.

3. *Pudendal nerve somatosensory evoked potential*

The cortical somatosensory evoked potential (SSEP) was recorded using 2 silver disc electrodes attached to the scalp. After the scalp had been cleaned and gently abraded to improve conduction, the electrodes were attached to the skin with collodion, and conducting NaCl jelly was introduced through a small hole in the top of the electrode. The recording electrode was placed 2 cm behind the vertex (Cz-2 position), while the reference electrode was attached to the forehead, in the Fz position (Jasper, 1958). To minimise background myogenic interference during recording, the patients were asked to relax as much as possible, and in particular to close their eyes and to relax their jaw muscles.

A square-wave stimulus of 0.1 ms duration was applied to the dorsal nerve of the penis or clitoris as described above, at a frequency of 2 Hz. The stimulus intensity was 2.5 times the sensory threshold. Using a signal trigger and averaging technique, the response to a minimum of 128 stimuli was amplified and displayed on the recorder. If a clear response was not seen at this time, stimulation was continued until a maximum of 256 stimuli had been applied. The procedure was repeated at least once to ensure reproducibility and the average latency of the first positive (P1) peak was recorded.

4. *Motor evoked potential (MEP)*

A magnetic neural stimulator (Digitimer D190) was used. This machine provides a maximum output at the 100% setting of at least 1000 joules. Output was through a low impedance coil in the form of a figure of eight (designed by Professor P. Merton). Each loop had an internal diameter of 15 cm and an external diameter of 17 cm. As a safety precaution, magnetic stimulation was not undertaken if the subject had a cardiac pacemaker, or suffered from epilepsy, or had undergone previous intracranial surgery.

For cortical stimulation, the patient was asked to lie in a supine position while the coil was held over the scalp. The crosspiece of the coil was held with its centre approximately 2 to 4 cm behind the vertex and with the loops of the coil pulled down laterally on to the scalp. Stimuli were applied at a maximum rate of 1 every 3 s and the intensity of the stimulus was gradually increased until an EMG response was recorded in the urethral sphincter, or until the maximum output of the stimulator was reached. Responses were recorded initially with the patient relaxed, and then while the patient voluntarily contracted the sphincter. This was achieved by asking the patient to imagine that he/she was passing urine and then contract the muscle which would interrupt the flow.

For spinal stimulation the subject was asked to lie in the right lateral position. The coil was placed approximately 5 cm lateral to the lumbo-sacral vertebral column with the crosspiece of the coil perpendicular to the spinal cord. Again the stimulus intensity was gradually increased until an EMG response was recorded in the urethral sphincter or until the maximum output of the coil had been reached.

The concentric needle electrode in the urethral sphincter recorded the EMG response to stimulation via a trigger mechanism. The response was displayed in a falling leaf format on the electrophysiological recorder and for each coil position, 2 or more recordings were made to ensure reproducibility. The shortest latency of the onset of evoked sphincteric EMG activity was then measured.

B. Urodynamic Investigations

Standard urodynamic studies were performed, although X-ray screening was not available and there were several modifications of technique as suggested by Thomas (1979). After voiding freely, a filling catheter was inserted but the bladder was not emptied. The bladder was filled at a constant rate of 30 ml/s while intravesical and intrarectal pressures were recorded. A routine voiding study was then performed. All studies were repeated at least once (at the same sitting) to ensure reproducibility and the mean values were calculated for each parameter.

In addition, synchronous sphincter EMG recordings were made in all patients, using either a needle electrode in the anal sphincter or an anal plug electrode. In preliminary studies we had found that synchronous urethral recordings were difficult to perform because urine and saline often leaked on to the electrode and interfered with the EMG signal. Accordingly, we opted to record from the anal sphincter, which was the most practical alternative. There is some debate as to whether this approach is valid (Nordling and Meyhoff, 1979), although Anderson and Bradley (1976) found that the EMG activity in the urethral sphincter was similar to concurrent activity in the anal sphincter.

C. Statistical Methods

The mean motor unit durations and amplitudes were compared with control values by a simple *t* test. The numbers of polyphasic motor units in each group were compared using the chi-squared test, and the evoked potentials and the urodynamic findings were compared with control values using the Mann Whitney U test. Reference ranges for the control subjects were calculated using the formula (Reference range = Mean ± 2 Standard Deviations).

Ethical committee approval was obtained for this study from both St Bartholomew's Hospital and The National Hospital for Nervous Diseases.

Results

1. Urethral sphincter EMG

Studies in control subjects revealed a mean motor unit duration of 6.3 ms (SD 2.6) and a mean motor unit amplitude of 0.42 mvolts (SD 0.34). Only 5% of the motor units were polyphasic.

Urethral sphincter EMG was undertaken successfully in 23 of the patients with multiple sclerosis. One female patient was unable to tolerate the needle electrode despite the use of 2% lignocaine gel. In another female patient complex repetitive discharges (Fowler and Kirby, 1985) were heard throughout the urethral sphincter, precluding motor unit analysis.

As a result, motor unit analysis was performed in 22 of the 24 patients, and 193 motor units were isolated and analysed. The mean duration of the motor units in the patients with multiple sclerosis was 6.25 ms (SD 3.22) and the mean motor unit amplitude was 0.29 mvolts (SD 0.2). There was no statistical difference between the mean motor unit duration or amplitude of the control patients and those with multiple sclerosis.

A total of 23 motor units (11.9%) had a polyphasic waveform. Of these, 7 were found in a 20-year-old mother of 2 children. Labour had been prolonged in both births and in one case forceps delivery had been necessary. Using the chi-squared test there was a significantly increased number of polyphasic motor units in the patients with multiple sclerosis when compared with the control subjects ($P < 0.05$).

2. Sacral reflex latency

By the technique used in this study we were unable to record a sacral reflex response in any of the female patients, including both the control subjects and the patients with multiple sclerosis.

In the control male subjects (n = 8) the mean latency was 32.1 ms (SD 3.41), giving a normal range of 25.3 to 38.9 ms. In the men with multiple sclerosis (n = 9), the mean latency was 35.3 ms (SD 7.06). One patient had a giant response with a latency below the lower limit of the reference range, while 3 patients had latencies greater than 38.9 ms (Fig. 1).

There was no significant difference between the latency of the responses in the control subjects and the patients with multiple sclerosis.

3. Somatosensory evoked potential

In the control patients (n = 11) a response was recorded in all patients. The mean latency of the first positive (P1) potential of the evoked potential was 39.0 ms (SD 3.24), giving a normal range of 32.5 to 45.4 ms.

In 12 of the patients with multiple sclerosis no response could be recorded; of the others, 9 had P1 latencies greater than 45.4 ms. In only 3 patients was the P1 latency within the normal range. If it is assumed that an absent response indicates abnormality, then in this study 88% of the patients with multiple sclerosis had an abnormal somatosensory evoked potential (Fig. 2).

The normal SSEP responses were recorded in patients with Kurtzke grades of either 2 or 3, while

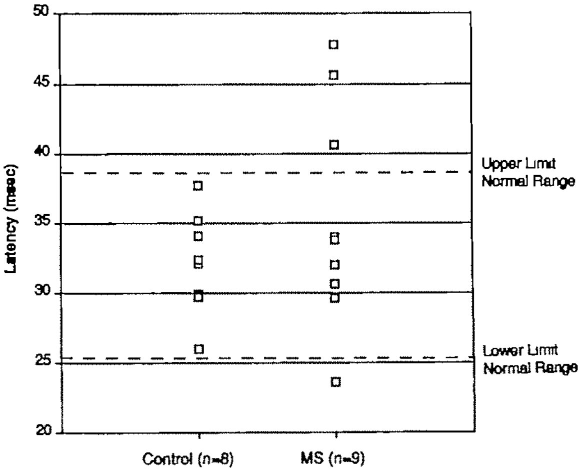

Fig. 1 Comparison of sacral reflex latencies of patients with multiple sclerosis and control values.

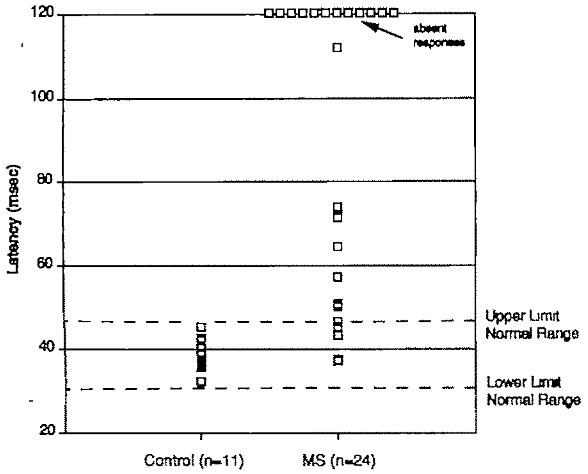

Fig. 2 Comparison of pudendal nerve cortical somatosensory evoked potentials of patients with multiple sclerosis and control values.

the abnormal responses were typically found in those patients with more severe disability.

4. *Motor evoked potential*

In the control subjects the response with the shortest latency was that obtained following cortical stimulation with slight voluntary contraction of the striated urethral sphincter (otherwise called the facilitated response). The mean value of the latency of this response was 26.4 ms (SD 2.21). This gives a normal range of 22.0 to 30.8 ms.

Ten patients with multiple sclerosis were studied in this way.

(a) Cortical stimulation. In general, the stimulator had to be at maximum output in order to obtain an EMG response, and in only 2 patients was it possible to obtain a response in the urethral sphincter without facilitation. Both of these patients had mild clinical disability (associated with Kurtzke grade 2).

With voluntary contraction of the sphincter, a response was recorded in 5 subjects. One patient had a latency just below the lower limit of the normal range, 2 had responses within the normal range and 2 had responses with a prolonged latency. All of these 5 patients had relatively mild disability associated with Kurtzke grades 2 or 3.

In the other 5 patients no response could be detected even with voluntary contraction of the sphincter (Fig. 3).

(b) Spinal stimulation. A response was recorded to spinal stimulation in 4 patients and all of these responses had latencies within the reference range. Of these patients, 2 had prolonged cortical latencies, from which it can be concluded that the conduction defect lay within the central nervous system.

5. *Urodynamic studies*

The results for the patients with multiple sclerosis are detailed below, and using the Mann Whitney U test were compared with the control group (for each value, the median, the range and the level of significance are included).

The median initial residual volume was 45 ml (range 0–390 ml, NS); on filling, the subtracted intravesical pressure rose to a raised level of 12 cm of water at the end of filling (range 2–100 cm water, $P < 0.01$). The maximum filling pressure was also raised at 32 cm of water (range 2–100 cm water, $P < 0.01$) and the bladder capacity was low at 300 ml (range 30–915 ml, $P < 0.05$).

On voiding, the volume voided was also low at 200 ml (range 0–760 ml, $P < 0.001$) with a low peak flow rate of 14 ml/s (range 0–39 ml/s, $P < 0.001$) and a peak voiding pressure of 53 cm of water (range 3–102 cm of water, NS). The median residual volume at the end of the study was 70 ml (range 0–440 ml, $P < 0.05$).

Of the 24 patients studied, 15 had evidence of detrusor hyper-reflexia and 3 had detrusor areflexia (they had Kurtzke grades 4, 5 and 6 respectively). Six patients had essentially normal urodynamic studies with no evidence of either hyper-reflexia or areflexia, although 1 of them had stress incontinence and another had sensory urgency. All of these patients had a Kurtzke grade 2 or 3.

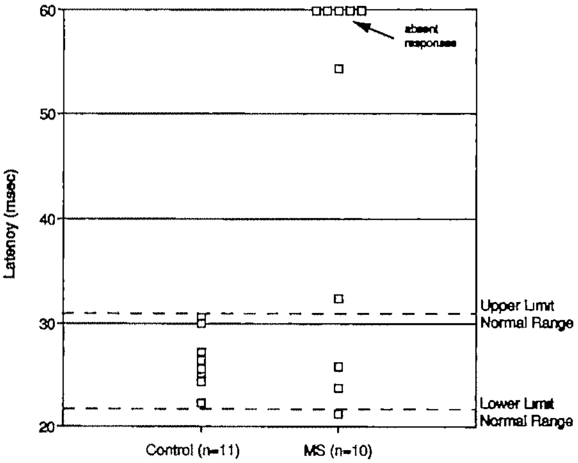

Fig. 3 Comparison of urethral sphincter motor evoked potentials of patients with multiple sclerosis and control values.

Table 2 Comparison of Pudendal Nerve Somatosensory Evoked Potentials and Urodynamic Findings in Patients with Multiple Sclerosis

Urodynamic findings	*Normal response*	*Delayed response*	*Absent response*
Stable (n = 6)	3	2	1
Hyper-reflexia (n = 15)	0	7	8
Areflexia (n = 3)	0	0	3
Dyssynergia (n = 4)	0	3	1
Normal relaxation (n = 4)	1	1	2

Table 3 Comparison of Urethral Sphincter Cortical Evoked Potentials and Urodynamic Findings in Patients with Multiple Sclerosis

Urodynamic findings	*Normal response*	*Delayed or absent response*
Stable (n = 3)	3	0
Hyper-reflexia (n = 5)	0	5
Areflexia (n = 2)	0	2
Dyssynergia (n = 2)	0	2
Normal relaxation (n = 2)	1	1

On the whole, attempts at synchronous sphincter EMG were technically unsatisfactory, but 4 patients were shown to have evidence of detrusor-external sphincter dyssynergia associated with detrusor hyper-reflexia. In 4 patients the sphincter EMG was judged to have a normal pattern (2 of these patients had hyper-reflexia, 1 had a stable bladder and 1 had detrusor areflexia).

Comparison of the urodynamic and neurophysiological results for each patient is shown in Tables 2 and 3. Patients who had essentially normal urodynamic studies usually had normal somatosensory and motor evoked potentials, while patients with hyper-reflexia, areflexia or dyssynergia usually had evidence of abnormal central motor and sensory conduction.

Discussion

The urodynamic findings in this study are similar to the findings in previous reports and show that in patients with multiple sclerosis, the majority have detrusor hyper-reflexia (with or without detrusor-external sphincter dyssynergia), a proportion have detrusor areflexia, and some have "normal" studies (Bradley *et al.*, 1973; Blaivas *et al.*, 1979).

The finding of an increased number of polyphasic motor units in the patients with multiple sclerosis was unexpected. Goldstein *et al.* (1982) observed polyphasic pelvic floor action potentials in 34% of their patients with MS and detrusor hyper-reflexia. They argued that this represented evidence of multilevel disease, since the hyper-reflexia indicated suprasacral demyelination while the abnormal motor units indicated sacral cord involvement. A second possible explanation is that since the multiple sclerosis group contained a higher proportion of women than the control group, other factors (such as childbirth) which are known to affect the duration and polyphasicity of motor units within the pelvic floor (Allen *et al.*, 1988) could have produced this finding.

The former explanation is supported by studies on sacral reflex latencies. Goldstein *et al.* (1982) found that of 23 men with multiple sclerosis and urinary disorders, 35% had a delayed sacral reflex response. Tackmann *et al.* (1988) also found abnormal sacral reflex responses in a group of multiple sclerosis patients with impotence and we found 3 men in this study (all of whom were impotent) who also had a prolonged sacral reflex latency. In 2 men this was related to detrusor hyper-reflexia (1 of whom had detrusor-external sphincter dyssynergia) and in 1 man the urodynamics showed no abnormality. In the former study of sacral reflex latencies mentioned above, there were no reports of abnormalities in women, and indeed we found technical difficulties in recording a response in women. However the results were reproducible in the men and presumably represent significant conduction abnormalities.

From the EMG studies and from the studies of sacral reflex latencies, there is thus neurophysiological evidence of sacral demyelination in a proportion of patients with multiple sclerosis and voiding disorders, which may or may not contribute to the urodynamic picture seen in these patients. Pathologically, Philp *et al.* (1981), when reviewing the pathological specimens which had originally been described by Oppenheimer (1978), showed that sacral demyelination was present in only 18% of patients with multiple sclerosis. Although the short unmyelinated interneurones of the sacral reflex arc cannot be affected by the demyelinating process, it is possible that a plaque in ascending or descending myelinated fibres of the sacral cord could interfere with conduction in either the afferent or efferent limb of the reflex arc. This might produce a delayed sacral reflex response and might also cause polyphasic motor unit potentials to be present within the striated urethral sphincter.

In 1 young woman we found complex repetitive discharges and decelerating bursts (CRD and DBs). This activity has been reported in a group of young women with urinary retention, none of whom had neurological disease (Fowler *et al.*, 1988). However, there are reports in the literature of CRD and DBs being present in patients with a variety of neurological diseases including multiple sclerosis (Potenzoni *et al.*, 1983). Our patient had predominantly retentive symptoms, although on urodynamic testing she had detrusor hyper-reflexia.

Abnormal somatosensory evoked potentials are a common feature of multiple sclerosis (Namerow, 1968; Trojaborg and Petersen, 1979), although these studies have concentrated on potentials produced by stimulation of the median nerve, posterior tibial nerve and common peroneal nerve. In Trojaborg and Petersen's study, the common peroneal response was abnormal in 82% of subjects, compared with 62% for the median nerve. There are few reports of the somatosensory response to pudendal nerve stimulation in multiple sclerosis, although Haldeman *et al.* (1982) found that in 3 patients with multiple sclerosis and bladder dysfunction the pudendal nerve SSEP was invariably abnormal. Tackmann *et al.* (1988) found that 5 of 7 impotent men with multiple sclerosis had delayed or absent pudendal nerve SSEPs. Of the patients with multiple sclerosis in this study, 88% had an abnormal response and in most cases (83%) this was associated with urodynamic evidence of urethrovesical dysfunction.

Several studies have shown delay in the motor evoked potentials to the arm (Hess *et al.*, 1987) and leg (Ingram *et al.*, 1988) in patients with multiple sclerosis. These studies showed that often there was evidence of delayed motor conduction in patients with normal clinical findings although, in general, central motor conduction times were directly related to functional motor disability. Of the 10 patients in this study, the facilitated cortical conduction time was delayed or absent in 7. Furthermore, both the normal and the delayed responses were found in those patients with relatively low Kurtzke grades, while absent responses (indicating a conduction block) were usually associated with a relatively high degree of disability.

What then is the relationship of these neurophysiological abnormalities to the presence or absence of urethrovesical dysfunction? In this study, 6 patients, despite having urinary symptoms, had no urodynamic evidence of hyper-reflexia, areflexia or detrusor sphincter dyssynergia and it was in these patients that all of the normal urethral sphincter MEPs and pudendal nerve SSEPs were recorded. We would suggest that in these patients the urinary symptoms had a non-neurogenic basis.

In contrast, detrusor hyper-reflexia, areflexia and detrusor-external sphincter dyssynergia were invariably associated with abnormalities of the SSEP and the MEP. It is probable that somatosensory evoked potentials assess conduction in the dorsal columns (Jones and Small, 1978), while magnetic stimulation probably results in conduction within the corticospinal tract (Mills *et al.*, 1987). Although it is known that these pathways are probably not intimately related to the neural control of detrusor function, in this study abnormalities in conduction within them did correlate quite well with the presence or absence of vesical dysfunction.

The motor tracts which have been tested in this study are, however, probably important in the neural control of the striated urethral sphincter. It has been suggested that detrusor-external sphincter dyssynergia is related to damage within the suprasacral spinal cord (Blaivas *et al.*, 1981) and some studies have demonstrated a relationship between DSD and extensor plantar responses (Goldstein *et al.*, 1982). In our study, 4 patients were found to have definite evidence of DSD and all had abnormalities of both motor and sensory conduction. However, 4 patients were found to have normal sphincteric relaxation and 1 of them had abnormalities of both sensory and motor pathways. The results of this study therefore suggest that detrusor-external sphincter dyssynergia does reflect disruption of the corticospinal tract, although conversely, damage to these neurones does not necessarily result in a measurable sphincteric abnormality.

In conclusion, this study shows that in patients with urodynamic abnormalities related to multiple sclerosis, there is commonly neurophysiological evidence of abnormalities of both motor and sensory conduction. Furthermore, we have been able to demonstrate that in a small proportion of these patients there is neurophysiological evidence of disease within the sacral spinal cord, in addition to the more common suprasacral demyelination.

Acknowledgements

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Treatment of Recurrent Urethral Strictures Using Clean Intermittent Self-catheterisation

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Summary—The treatment of urethral strictures has been greatly improved by the use of the optical urethrotome. However, there remains a group of patients with recurrent strictures for whom the alternatives remain long-term dilatation/urethrotomy or urethroplasty.

Over the last 3 years we have treated 65 such patients using clean intermittent self-catheterisation as a method of self-dilatation. This has resulted in a dramatic decrease in the number of operations performed on these patients, with no significant reduction in urinary flow rate over an average follow-up period of 20 months.

The method offers the possibility of long-term cure and should be offered to all such patients, reducing still further the number of patients who require urethroplasty.

The problem of urethral stricture has been one that has vexed practitioners for centuries. Blind urethrotomy and intermittent dilatation results in a high rate of complications (Blandy, 1980) and necessitates treatment at frequent intervals for years, often a lifetime. Urethroplasty using skin flaps (Blandy, 1975) seemed to offer better long-term results, but even in skilled hands it has a significant complication rate (Blandy *et al.*, 1976), including recurrent stricturing, and may involve more than one major operation for an elderly patient.

The procedure described by Sachse (1974), using a cold-knife optical urethrotome to incise the stricture at 12 o'clock under direct vision, has gained wide-spread acceptance as a result of its low mortality and morbidity, short hospital stay and the fact that even repeated procedures do not compromise secondary urethroplasty. The main complication is recurrent stricture. Cure rates vary from 81% (Gaches *et al.*, 1979) to only 25% (Boccon Gibod and Le Porte, 1982) at 2 years and are not improved by the use of indwelling catheters or by hydraulic self-dilatation. Most studies have shown that those strictures which recur are less likely to be cured by subsequent urethrotomies (Holm-Nielsen *et al.*, 1984), leading to the suggestion that after 2 or 3 urethrotomies, urethroplasty should be considered (Mundy and Stephenson, 1988).

There is clearly a place for a simpler form of therapy in those patients who require repeated treatment for their stricture and for the last 3 years we have taught them a method of self-dilatation, applying the principles of clean intermittent self-catheterisation (CISC) (Lancet, 1979). First described by Lapides *et al.* (1972), the method has revolutionised the care of patients with neurogenic bladders (Lapides *et al.*, 1976). It is easy to teach to patients of all ages (Hannigan, 1979; Whitelaw *et al.*, 1987) and is associated with few complications (Maynard and Diokno, 1984; Klein *et al.*, 1986).

Catheters for use in this manner are prescribable on the National Health Service and have a surface coating of a hydrophilic polymer designed to self-lubricate when dipped into water (LoFric catheters, Astra Meditec Ltd, Stroud).

Patients and Methods

Between October 1986 and February 1989, 64 men and 1 woman with recurrent urethral strictures commenced CISC, using disposable LoFric catheters. Their ages ranged from 8 to 90 years (mean

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56.6), with a total of 491 documented operations for urethral strictures (an average of 1 procedure every 6.3 months). Patients included in the study had to have had at least 1 recurrence of their stricture (n = 25) and 1 patient had had 50 procedures.

All patients underwent initial assessment 3 to 5 days after their last operation, the aetiology, position of the stricture (Fig. 1) and latest method of treatment being noted; 26 patients had had a urethral dilatation, 26 a visual urethrotomy using the Storz urethrotome, 12 required both and 1 patient needed a bladder neck resection in addition to a dilatation. A maximal flow rate was recorded (Smith, 1966; Shoukry *et al.*, 1975) before entry to the study.

Each patient was then taught how to use the LoFric catheters using the clean method described by Lapides *et al.* (1972) and explained more fully in the "*Patient Guide to Intermittent Self-catheterisation with LoFric*" (Astra Meditec Ltd). Many found the process easiest in the bath, tap water being used to lubricate the catheter. A minority of patients found the lignocaine gel helpful initially.

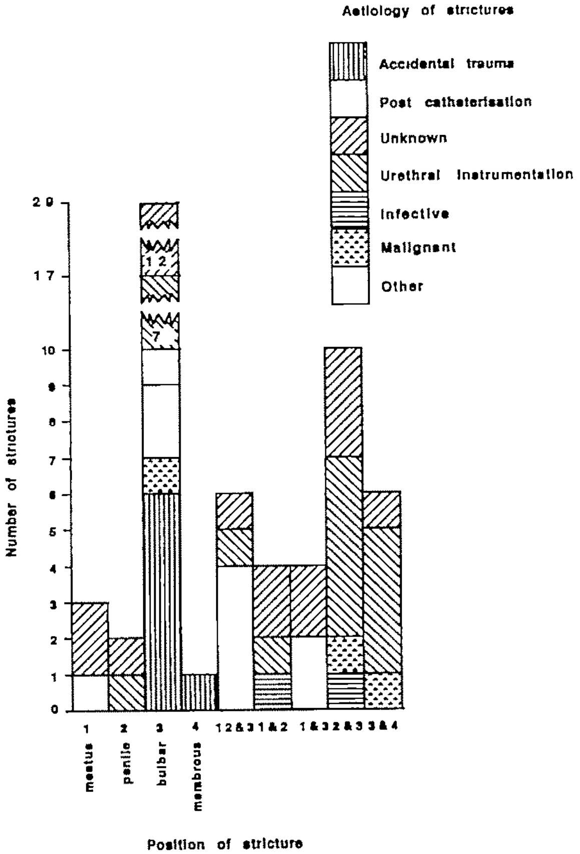

Fig. 1 Position and aetiology of strictures.

Table 1 Catheter Sizes

Catheter size	18F	16F	14F	12F	10F
No. of patients	49	9	4	2	1

The largest catheter which could be comfortably passed as far as the bladder (to drain urine) was used (Table 1). The 8-year old boy was taught using a size 10F.

At the initial assessment 56 patients found the passage of the catheter easy and only 9 had any difficulty, usually due to visual or physical handicaps. No patient was unable to use the catheters.

The patients were supplied with catheters of the appropriate size and instructed to pass one twice a week (every Wednesday and Sunday) for 4 weeks and then on a weekly basis for a further 5 months. After this they were allowed to decrease the frequency of CISC according to their symptoms. They were reviewed after the first month and then at intervals of 2 or 3 months. At each visit symptoms of outflow obstruction, problems with CISC and a flow rate were recorded.

Results

Sixty patients remain under follow-up; 1 patient developed renal failure secondary to tuberculosis (patient A), 1 had a urethroplasty (patient B) and 3 died of unrelated causes. The average length of follow-up was 20.5 months (range 8–38).

Flow rates were measured in 59 patients both at their initial assessment and their most recent follow-up. Of the other 6, 1 failed to produce an initial flow rate and 5 were contacted by telephone for their most recent follow-up, 3 being unfit to travel and 2 having moved from the area.

Comparison of the initial and most recent flow rates showed a significant correlation of 0.632 ($P < 0.001$). The initial average flow rate of 23.2 ± 14.5 ml/s fell slightly to a current mean of 20.0 ± 12.0 ml/s. The mean change in flow rate was a fall of 3.17 ± 11.56 ml/s, but the paired Student's *t* test showed no significant change in flow rate over the follow-up period ($0.5 > P > 0.1$).

The current rate of CISC is shown in Figure 2 and excludes patients A and B; 17 patients have not used the catheters for an average of 12.0 months and remain symptom-free.

Complications occurring during the study period are shown in Table 2. Eight of the 9 patients with recurrent strictures failed to attend a follow-up

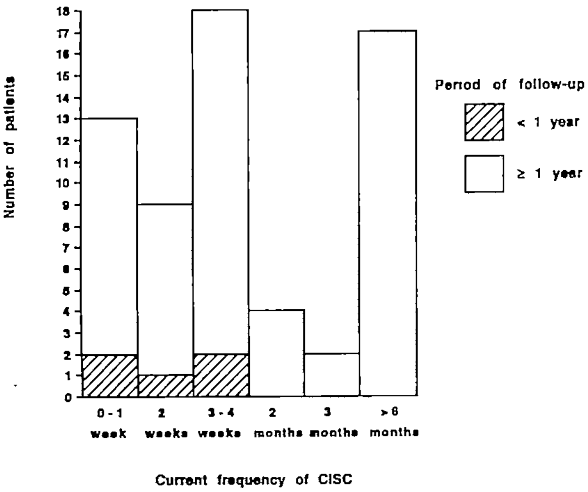

Fig. 2 Current frequency of clean intermittent self-catheterisation.

appointment prior to developing recurrent obstructive symptoms. They resumed CISC following surgical treatment of their stricture and have had no further problems. The ninth case (patient B) had recurrent dysuria and pain while using CISC over a period of 20 months, with 3 episodes of urinary tract infection (UTI). He was treated successfully by urethroplasty.

Eight other patients have required occasional check cystoscopies for bladder tumour follow-up. All have apparently normal urethras on urethroscopy.

Symptomatic inquiry during CISC revealed 3 patients with persisting obstructive symptoms, 2 (including the only female) with occasional incontinence and 1 with frequency.

A total of 56 patients (86%) found the method "very satisfactory", 5 were equivocal and only 4 were unhappy. The latter group included 2 patients who experienced pain on CISC, 1 who had a recurrent stricture and 1 who had 4 episodes of UTI. Patients' unsolicited comments ranged from "an absolute Godsend" to "barbaric".

Table 2 Complications

Complications	*No of episodes*
Recurrent stricture	9
Urinary tract infection	11
Bleeding	3
Pain using catheters (no of patients)	2
Epididymo-orchitis	2

Discussion

During the course of the study the average period between surgical treatments rose from 6.3 to 148.1 months and there was no significant change in the average flow rate, which remained within the accepted normal range.

CISC is widely acceptable to patients of all ages and requires no special expertise. Initially, however, they do require sympathetic and often repeated tuition to enable them to pass the catheters and the importance of frequent, well organised follow-up, particularly in the early months, is stressed by the fact that 8 of the 9 patients with recurrent strictures developed them after exhausting their supply of catheters.

After the initial 6-month period most patients felt happy using the catheters and they were allowed to vary the rate of usage according to a personal estimate of their urinary stream. Allowing them this discretion probably increased compliance, as the effect of passing the catheters was immediately obvious. The effect on the cure rate of such a policy, as opposed to a regimented one, is not known.

A total of 17 patients remain symptom-free and they have not used the catheters for more than 6 months, suggesting that the method is capable of producing prolonged symptom-free periods with good flow rates. CISC avoids the trauma and subsequent scarring caused by bouginage and urethrotomy. We believe this allows the urethra to heal with less tendency to restricturing, a belief supported by the normal appearance of the urethra in the few patients who have needed incidental cystoscopies.

These results, in a group of patients with often difficult and always recurrent strictures, suggest that this method should be considered as an alternative to urethroplasty or recurrent dilatations/urethrotomies. It avoids repeated hospitalisation and general anaesthesia, requires no special expertise, and thus has the potential for world-wide use.

We do not deny that some patients will eventually require urethroplasty but their numbers can be substantially reduced by using this method, which does not appear to interfere with subsequent urethroplasty should this become necessary.

Acknowledgements

We thank Mr J Gordon Smart and Mr D. E. Osborn for allowing us to include their patients in the study and we acknowledge the help of Mr R Kinder in the initiation of the study. Our thanks also go to Mrs Pamela Murray for her help in organising out-patient follow-up.

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PAEDIATRIC UROLOGY

Forced Hydration Prior to Renography in Children with Hydronephrosis. An Evaluation

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Summary—We have developed a method of diuretic renography for the assessment of upper urinary tract obstruction in children. A maximal diuresis under standardised conditions is obtained by forced intravenous hydration over a 2-h period prior to renography.

We evaluated the predictive value of this method for the clinical and functional outcome in 73 children with apparent unilateral pelviureteric junction obstruction. The predictive value of a non-obstructive pattern was 94%, while the predictive value of an obstructive pattern could not be assessed accurately because the patients concerned subsequently underwent operation. The method is safe and reliable and offers advantages over conventional diuretic renography.

Hydronephrosis due to pelviureteric junction (PUJ) obstruction is the most frequently encountered problem of obstructive uropathy in childhood. Prenatal diagnosis by means of ultrasound studies has considerably increased its detection in early childhood. It is still a matter of controversy which children will benefit from either surgical correction or from a more conservative approach. Several methods to differentiate between obstructive and non-obstructive PUJ have been described. Usually diuretic renography and pressure-flow studies are performed (O'Reilly *et al.*, 1979; Whitaker *et al.*, 1979) but it is well documented that the 2 methods do not accord in many patients, especially in those with only marginal obstruction (Whitaker and Buxton-Thomas, 1984; Kass *et al.*, 1985). This can be attributed in part to differences in urinary flow. Wacksman *et al.* (1986) showed that a suboptimal urinary flow can be insufficient to demonstrate the obstruction. In other cases where stasis in grossly dilated systems mimics obstruction, a suboptimal urinary flow may not be enough to demonstrate adequate drainage. In general, urinary flow is lower during renography than during pressure-flow studies despite the administration of a diuretic drug. Moreover, there is considerable variation in the diuretic response according to the state of hydration of the patient (Suki *et al.*, 1985), whereas the flow during pressure-flow studies is more or less standardised. Our method of hypotonic volume expansion prior to renography (HVE renography) was designed to overcome these problems by inducing a maximal and standardised urinary flow prior to renography. For practical reasons, especially where young children are concerned, we have chosen the intravenous route to secure a high fluid intake. Our methods and preliminary results have been reported elsewhere (Sukhai *et al.*, 1985, 1986).

In this study we present data on the predictive value, as derived from clinical follow-up data, in a group of patients thought to have unilateral PUJ obstruction.

Patients and Methods

Over a 5-year period 73 children with unilateral hydronephrosis were investigated. Eight had only 1 kidney. Those with a concomitant dilated ureter, vesicoureteric reflux or contralateral abnormalities were excluded. All patients were initially studied using ultrasound, intravenous urography and HVE frusemide renography. Based on these investigations and the clinical findings, they either under-

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went surgery or were treated conservatively and all were subsequently followed up for 12 to 78 months (mean 35). All patients received at least 1 repeat HVE frusemide renography study during the follow-up period.

Patients' characteristics are presented in Table 1. Their ages ranged between 0 and 14 years (mean 3.7). Males were more frequently affected than females at all ages (ratio 2.6:1), while a left to right preponderance was found more often in the younger children than the older ones ($P<0.05$: Fisher exact test). Twenty-nine patients showed no clinical symptoms on presentation. Detection was by prenatal ultrasound screening in 13 patients and by coincidence in patients with different kinds of renal and non-renal anomalies. The decision to operate was not associated with sex, age at diagnosis, site of the involved kidney or presenting clinical symptoms, except in those patients presenting with pain, who usually underwent surgery. Surgical treatment consisted of an Anderson-Hynes pyeloplasty, except for 3 patients who underwent nephrectomy because of a non-functioning kidney.

The procedure for HVE renography has been described in more detail elsewhere (Sukhai *et al.*, 1986). After an oral waterload (20 ml/kg), we infused hypotonic saline (0·45%) with dextrose (2·5%) in a dose of 2 L/1.73 m^2 BSA over a 2-h period. A ^{99m}Tc-DTPA renal scan was then performed and 30 min after administration of the isotope the patient was urged to empty the bladder and frusemide (0.3 mg/kg body weight) was administered intravenously. Some patients, especially the very young ones, failed to empty their bladder in time and in these cases the renogram continued as usual. It is our policy that only patients with reduced drainage of the upper urinary tract, in combination with bladder retention on the final pictures, are subjected to a repeat renogram with a bladder catheter *in situ*. In our patients this was never necessary. The function of individual kidneys as a percentage of total function was calculated from the uptake of the isotope during the second minute after injection. Excretion of the isotope before and after frusemide was determined visually and on the computer curves at 5-min intervals. Urinary drainage was determined by renography according to O'Reilly *et al.* (1979). At follow-up, changes of more than 10% of the initial individual function were considered significant.

Total renal function, with allowance for age, was expressed using a standard deviation score (sds) based on the normal values for age of plasma creatinine given by Schwartz *et al.* (1976, 1984). Changes during follow-up were evaluated statistically by means of Wilcoxon's signed rank test.

Results

A fluid load of 4% of body weight was well tolerated by all patients. The urine osmolality was usually between 40 and 65 mmol/L prior to the administration of frusemide. Table 2 shows the initial treatment of patients in relation to their first renogram.

The 33 patients with an obstructive pattern on the initial renogram were operated upon successfully, except for a mentally retarded boy whose parents refused the operation (Table 2). During follow-up the obstructive pattern remained unchanged in this child. His renal function, as determined by creatinine and renogram was, however, not significantly reduced. None of the

Table 1 Details of Patients

	Age at diagnosis			
	< 1 year		*> 1 year*	
Initial therapy	*Conservative*	*Surgery*	*Conservative*	*Surgery*
Male/female	10/5	11/4	14/6	18/5
Left/right	10/5	14/1	12/8	11/12
Presenting symptoms				
None	11	9	4	5
Urinary tract infection	3	5	9	5
Pain			5	10
Haematuria			2	3
Abdominal mass	1	1		
Total	15	15	20	23

Table 2 Initial Treatment following First Renal Scan

Initial renogram	*Surgery* −	+
Not obstructive	32	1
Equivocal	2	5
Obstructive	1	32

patients required a second operation. Their clinical symptoms disappeared except for 1 patient who had a urinary tract infection 1 year post-operatively. Urinary drainage as determined by HVE renography, as well as by ultrasound and intravenous urography, improved in all patients after pyeloplasty. The individual renal function of the involved kidney was assessed by renography in 27 patients. The contribution to total renal function improved on average from 36% pre-operatively to 43% post-operatively ($P<0.001$). An improvement of more than 10% of the initial contribution was noted in 13 patients, while no patient showed a deterioration of more than 10% of the initial individual function. As shown in Figure 1A, improvement was particularly evident in patients with moderate to severe initial impairment of renal function. For children with an individual renal function of less than 40% (n = 16) the mean percentage improved from 28% pre-operatively to 38% post-operatively ($P<0.001$). The mean percentage for the remaining children (n = 11) was 47% pre-operatively and 49% post-operatively (not statistically significant). Post-operative plasma creatinine was generally lower than the pre-operative values ($P<0.002$); 26 pa-

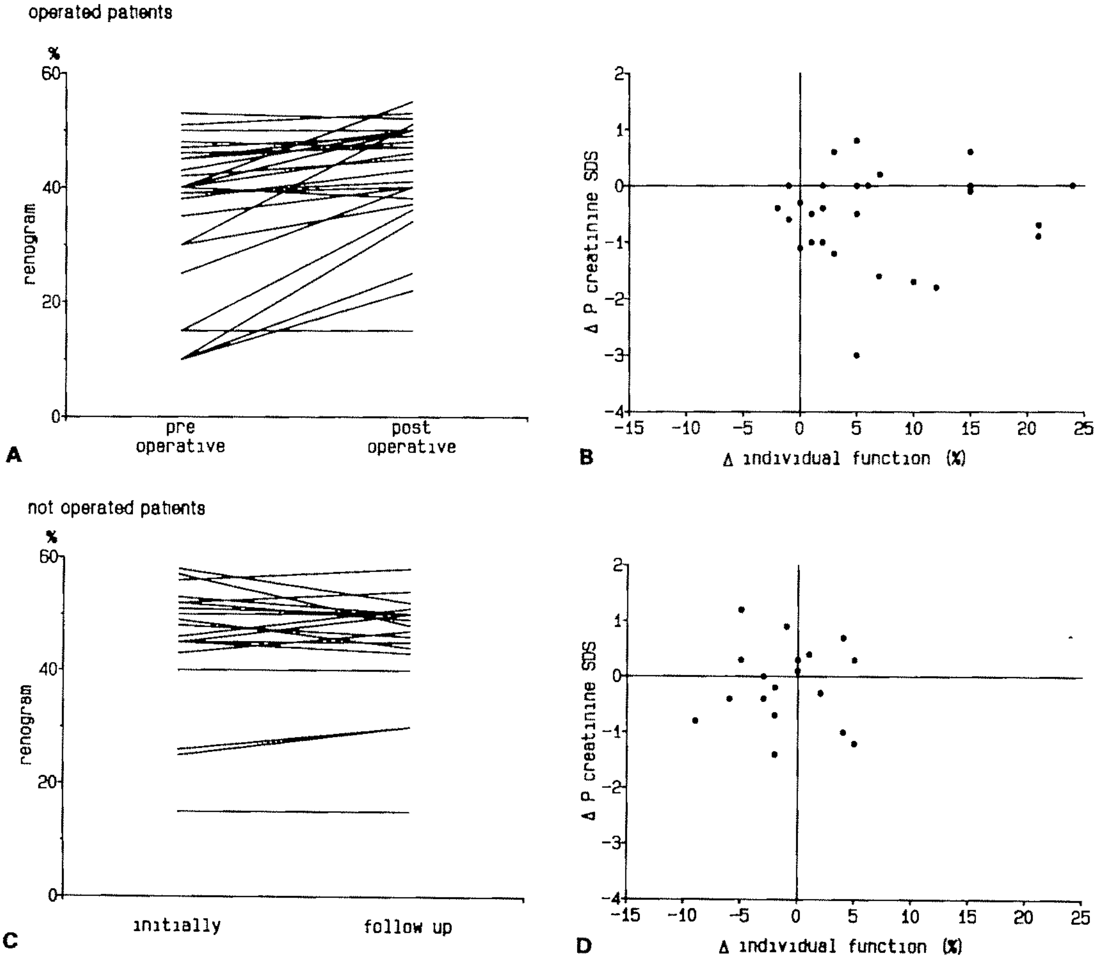

Fig. 1 Development of renal function in surgically treated (A, B) and conventionally treated (C, D) patients with unilateral hydronephrosis A and C show the contribution of the involved kidney to the total renal function on the renogram. B and D show the changes in total renal function, expressed as the change in the standard deviation score (△ SDS) for creatinine versus the change in individual renal function on the renogram, expressed in % of the total renal function

tients improved in their standard deviation score for creatinine and 6 did not ($P<0.002$). No correlation could be found between the change in plasma creatinine and the change in relative renal function on the renogram for individual patients (Fig. 1B).

The 33 patients with adequate drainage on the initial renogram did not undergo surgery, except for a boy with intermittent flank pain who had a successful pyeloplasty 2 months after the initial renogram (Table 2). The intermittent nature of this boy's obstruction was confirmed by successive sonograms showing clear dilatation only at moments of flank pain. Surprisingly, the clinical symptoms disappeared in all patients. Follow-up renography showed adequate drainage in all but 1 patient who subsequently underwent a pyeloplasty (Table 3). This patient had an asymptomatic non-obstructive hydronephrosis as a neonate and showed reduced drainage on the HVE renogram 1 year later, although a reduction in renal function of the involved kidney could not be demonstrated. Individual renal function as determined by renography and total renal function as determined by plasma creatinine concentration did not change in this group of patients (Figs 1C and D) and there was no correlation between these parameters. The predictive value of renography for adequate drainage was 94% (31/33).

Of the 7 patients with equivocal obstruction, 5 underwent an uncomplicated pyeloplasty for various clinical reasons. Of the 2 patients who were not operated upon, 1 proved to have adequate drainage during follow-up studies, while the other one remained equivocal (Tables 2 and 3).

Of the 8 patients with a solitary kidney, 7 were non-obstructive and were followed up conservatively, while 1 patient had a pyeloplasty because of an obstructive pattern on the renogram. None of these 8 patients had a significant change in renal function during follow-up, although their initial plasma creatinine was slightly elevated.

Table 3 Follow-up Renography of Patients Receiving Conservative Treatment Initially

Initial renography	*Follow-up renography*		
	Not obstructed	*Equivocal*	*Obstructed*
Not obstructed	31		1
Equivocal	1	1	
Obstructed			1

Discussion

We have concentrated our efforts towards achieving a high, standardised diuresis. Our regimen of fluid intake was tolerated well. A high urinary flow rate of 6 to 10 ml/min/kidney/1.73 m^2 was attained in this group of patients. This flow is comparable with that generally used during pressure-flow studies and consequently minimises the flow-related discrepancies between pressure-flow studies and diuretic renography. We regard the standardisation of the protocol to be of crucial importance to the interpretation of follow-up data. However, an evaluation of the benefit of this fluid load regimen as compared to conventional diuretic renography has not yet been carried out.

Although the high fluid intake was well tolerated in this group of patients it should be realised that all of them had normal, or near normal, overall renal function. It is our experience that special care should be taken to avoid fluid overload, especially in patients with bilateral disease or obstruction in a solitary kidney. In patients with a reduced glomerular filtration rate the fluid load should be adjusted accordingly, since free water clearance is directly related to this rate.

Care should be taken when justifying surgical intervention. All operated patients showed improved drainage after pyeloplasty. However, surgical reduction of the pelvis itself can mimic improved drainage since it reduces the dilatation and so improves the washout of tracer on the renogram. The relief of clinical symptoms is of minor value since identical symptoms in the non-operated patients also disappeared. The improvement in renal function justifies the surgical correction for the group as a whole. However, the benefit for individual patients could not be determined. It therefore remains questionable whether patients with reduced urinary drainage during conditions of maximal diuresis, but without a significant reduction in individual renal function, will benefit from surgical correction. On the other hand, the predictive value of a non-obstructive renogram can be estimated quite accurately and is high (94%). However, the fact that 2 of these 33 patients had to undergo surgery indicates the importance of careful follow-up investigations. Although the follow-up data on urinary drainage and on progress of renal function are satisfactory in this group of patients, it is difficult to say how long the follow-up should be in these growing children. Moreover, renal damage due to partial obstruction may develop slowly.

Finally, we would like to stress that our HVE renography does not make pressure-flow studies redundant. In our experience, however, the indication to perform them is limited mainly to patients with reduced renal function of the involved kidney, which makes interpretation of the renogram difficult.

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Case Reports

Spontaneous Regression of Metastatic Renal Carcinoma with Long-term Survival

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Some authors doubt if spontaneous regression of metastatic renal carcinoma ever occurs. Of 125 patients who underwent nephrectomy for metastatic renal carcinoma between 1972 and 1987 we found 2 with spontaneous regression of pulmonary metastases and subsequent long-term survival.

Case Reports

Case 1. I.W., a 58-year-old woman, was referred in September 1978 with a diagnosis of left renal carcinoma with a solitary right pulmonary metastasis. Investigations revealed a huge malignant renal tumour in the left upper pole, a large tumour thrombus in the left renal vein and a solitary pulmonary metastasis in the right lower lobe. Since no other metastases could be found a left radical nephrectomy was planned, to be followed by resection of the pulmonary metastasis at a second operation.

In October 1978 a left radical nephrectomy together with para-aortic lymphadenectomy was performed. The spleen was also removed. The resected kidney contained a renal carcinoma 6 cm in diameter. The tumour had invaded the renal capsule and renal vein. Histological examination confirmed clear cell renal carcinoma infiltrating the renal capsule, renal pelvis and left adrenal gland and spreading to the hilar and para-aortic lymph nodes.

Post-operative chest X-ray revealed (in contrast to the pre-operative chest X-ray) an additional small right pulmonary metastasis just above the diaphragm (Fig. 1). Because of this metastatic progression the thoracic operation was cancelled.

The patient was discharged 28 days post-operatively without adjuvant therapy. However, follow-up at 3-monthly intervals showed that the patient had gained 1 kg in weight; the first pulmonary metastasis, which had been 3 cm in diameter, had shrunk to 1.5 cm and the second smaller metastasis had disappeared (Fig. 2). Three months later the patient was found to be in good condition; she had gained another 5 kg, the first pulmonary metastasis had also disappeared (Fig. 3) and she even wanted to start work again. In August 1989 the patient remained well and had no evidence of disease.

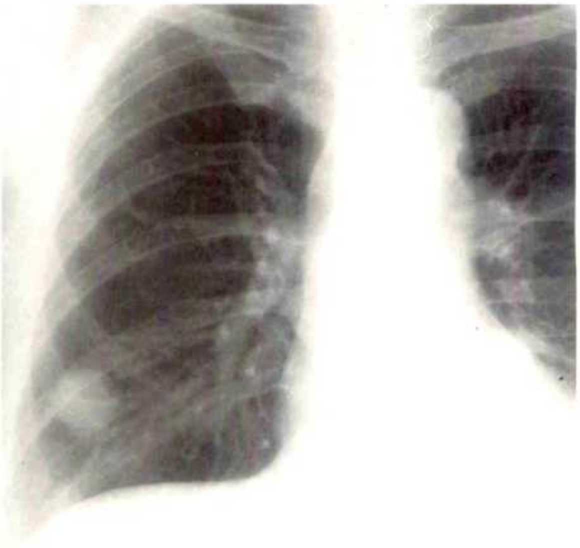

Fig. 1 23.10.78: 20 days post-operatively a second pulmonary metastasis is visible in the right phrenic angle.

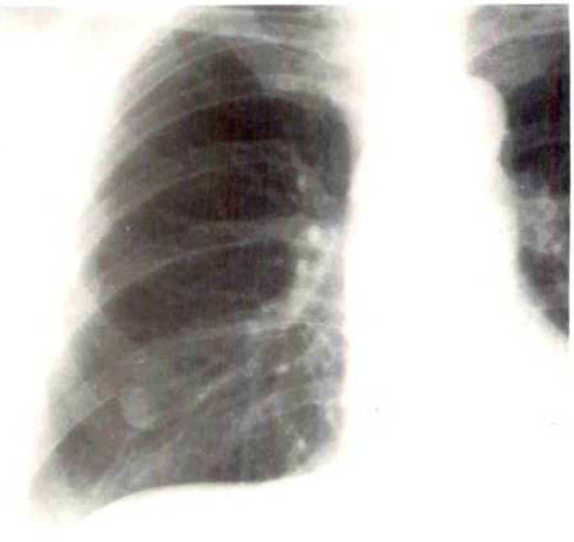

Fig. 2 13.12.78: 3 months post-operatively the second metastasis has vanished and the first has shrunk to 1.5 cm.

Case 2. K.R., a 45-year-old woman, presented in April 1984 with multiple pulmonary metastases (Fig. 4). CT scan revealed a 6-cm left renal tumour with enlarged para-aortic lymph nodes. Palliative hormonal treatment commenced in May 1984 with an 8-week course of tamoxifen 30 mg/day.

In June 1984 re-staging revealed almost complete regression of metastatic disease. CT scan of the thorax

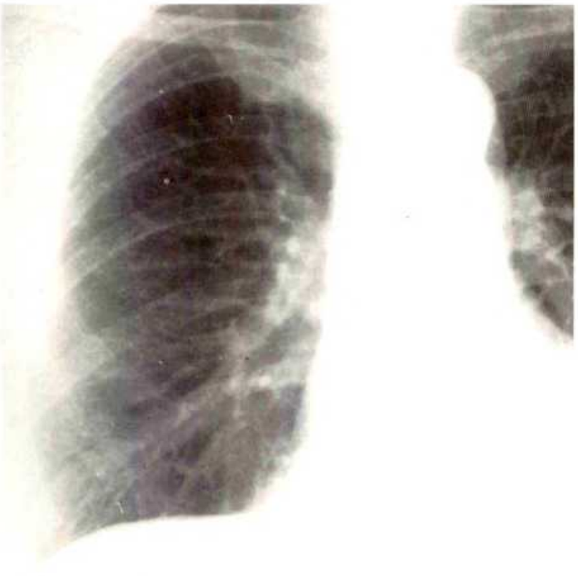

Fig. 3 14.03.79: 6 months after nephrectomy both metastases have disappeared.

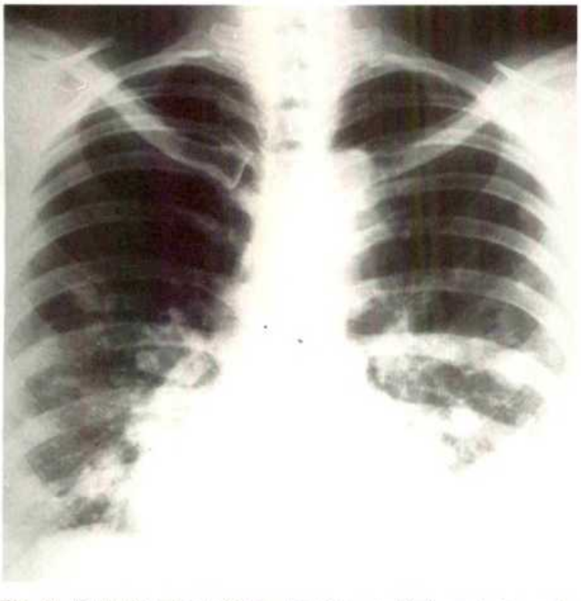

Fig. 4 13.04.84: chest X-ray showing multiple metastases in both lungs, especially on the right side.

showed 3 residual pulmonary metastases in the right upper zone and another one in the left lower zone; chest X-ray revealed only 2 residual metastases in the right mid-zone (Fig. 5). Abdominal ultrasound showed a reduction in size of the formerly enlarged lymph nodes. After further investigation by means of intravenous urography, reno-vasography, cavography and bone scan, a left transperitoneal radical tumour nephrectomy and retroperitoneal lymphadenectomy were performed in July 1984.

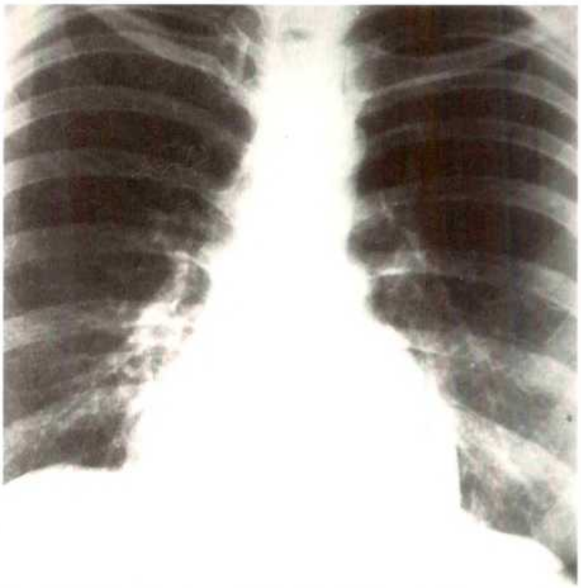

Fig. 5 27.06.84: chest X-ray after 2 months' treatment with tamoxifen showing small residual lesions at the site of former large metastases with obvious regression of metastatic disease.

Macroscopically the 6-cm tumour seemed to have infiltrated the renal capsule and pelvis. Histological examination revealed a high grade (G3) renal carcinoma with extensive necrosis. The hilar and para-aortic lymph nodes that had been enlarged on the abdominal CT scan also showed regression.

The patient made an uneventful recovery and was discharged home 11 days post-operatively. She continued to take tamoxifen 30 mg/day. In December 1984 she showed considerable improvement. Only 3 small pulmonary metastases remained and they could be seen only on a thoracic CT scan (they were not visible on chest X-ray) (Fig. 6). When seen in August 1989 she was free of disease; her drug regime was tamoxifen 10 mg/day.

Comment

Renal carcinoma is an unpredictable tumour. In 1986 the number of spontaneous regressions of metastatic renal carcinoma amounted to 80, of which only 15 had been histologically or cytologically documented (Kavoussi *et al.*, 1986). Other authors report different figures, but the number of histologically proven cases is always $<33\%$ and spontaneous regression of metastatic renal carcinoma appears to be $\leqslant 1\%$ (Snow and Schellhammer, 1982). We have found 2 cases of spontaneous regression of pulmonary metastases from a total of

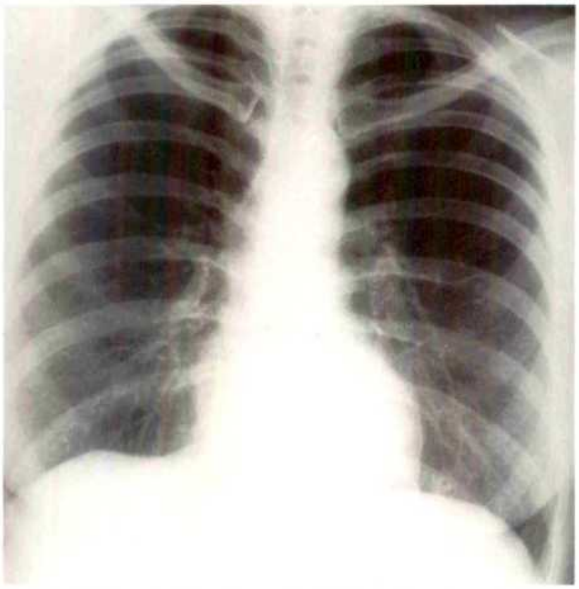

Fig. 6 19.11.84: chest X-ray 4 months after tumour nephrectomy. No sign of pulmonary metastases.

125 patients with metastatic renal carcinoma who underwent nephrectomy between 1972 and 1987.

Is aggressive management of metastatic renal carcinoma justified? In 1983 de Kernion stated, "However, patients who have solitary metastases, those who agree to participate in clinical trials involving nephrectomy and, perhaps, those who have large tumours with limited metastases especially to the lung or skin, may be reasonable candidates for this approach." Klugo *et al.* (1977), who experienced good results with radical nephrectomy and adjuvant hormonal chemotherapy, stated, "The management of solitary metastatic nodules should involve aggressive resection of the primary and metastatic nodule. Adjuvant hormonal and non-hormonal chemotherapy should be considered at all stages of the disease." We feel that our 2 cases demonstrate that aggressive treatment can be worthwhile.

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Retrovesical Hydatid Causing Haemospermia

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Hydatid disease is relatively uncommon in the United Kingdom (approximately 50 new cases/year) and involvement of the urinary tract is rare.

Case Report

A 68-year-old man presented in 1989 with a 7-month history of haemospermia, testicular and perineal pain without other urinary symptoms. He denied exposure to sheep or dogs but had been in North Africa in the war. He had previously had operations for hepatic hydatid in 1956 and 1987 (Fig. 1).

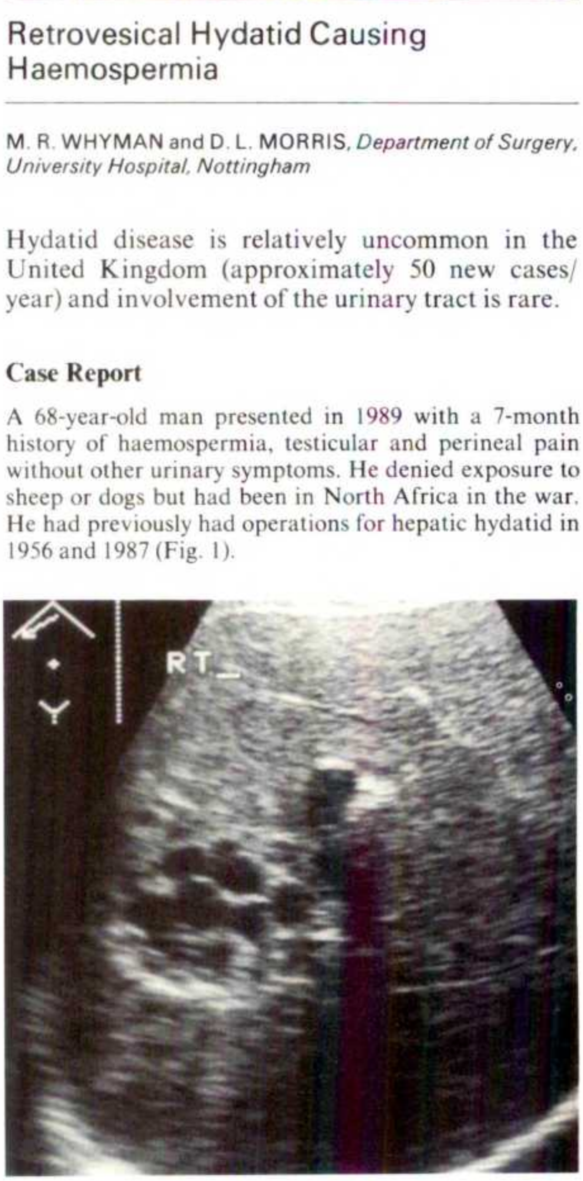

Fig. 1 Ultrasound scan showing hydatid cyst of right lobe of liver with many daughter cysts within.

A CT scan demonstrated a pelvic mass (Fig. 2) and examination under anaesthesia revealed a hard mass on the right side, extrinsic to the rectum, at the fingertip. The mass was confirmed by endoluminal ultrasonography. At laparotomy a tense cyst was found below the pelvic peritoneum firmly adherent to the right seminal vesicle, and the 2 were removed (an interesting incidental finding was a small mass in the pancreas, initially thought to be hydatid but histology after excision showed it to be a completely excised neuro-endocrine carcinoma). Histology showed a 5 × 4 × 3 cm pelvic hydatid containing daughter cysts, firmly adherent to the right seminal vesicle with blood in its lumen. The patient made an uneventful recovery and was well and symptom-free at follow-up 2 months later.

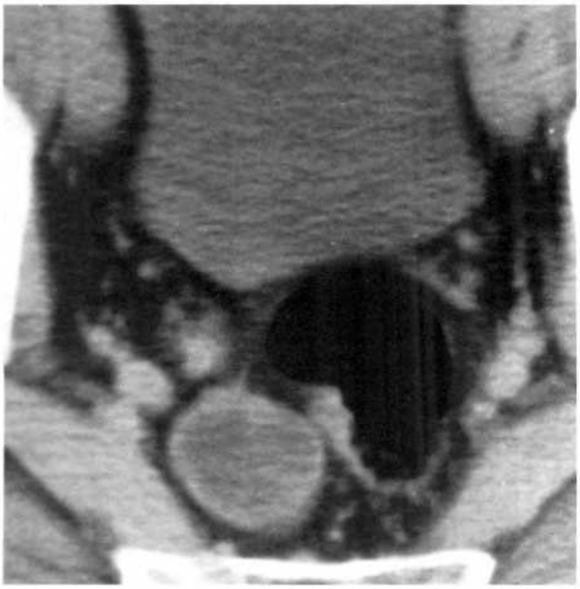

Fig. 2 CT scan of pelvis showing right pararectal mass.

Comment

The treatment of hydatid disease remains essentially surgical, although recent progress has been made in chemotherapy of this disease. We avoided pre-operative needle aspiration on biopsy of this mass because of the risks of anaphylaxis and dissemination. Urinary tract involvement occurs in only about 2% of all hydatid disease (Halim and Vaezzadeh, 1980) and most of these are renal. Echinococcal cysts have been reported involving seminal vesicles (Deklotz, 1976) and causing obstructive azoospermia (Rao, 1979). Haemospermia has not, however, been previously reported as a presenting feature of hyadatid disease.

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Rupture of False Aneurysm Secondary to Passage of Ureteric Stent

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We report the first case of rupture of a false aneurysm of the iliac artery due to retrograde passage of a ureteric stent.

Case Report

A 74-year-old man presented with a 4-day history of left loin pain. A left common to external iliac short segment bypass graft (8 mm Dacron) had been inserted 14 years previously. An abdominal ultrasound scan demonstrated a large iliac false aneurysm causing left hydronephrosis. These findings were confirmed by a left femoral arteriogram (Fig. 1) and an intravenous urogram demonstrated

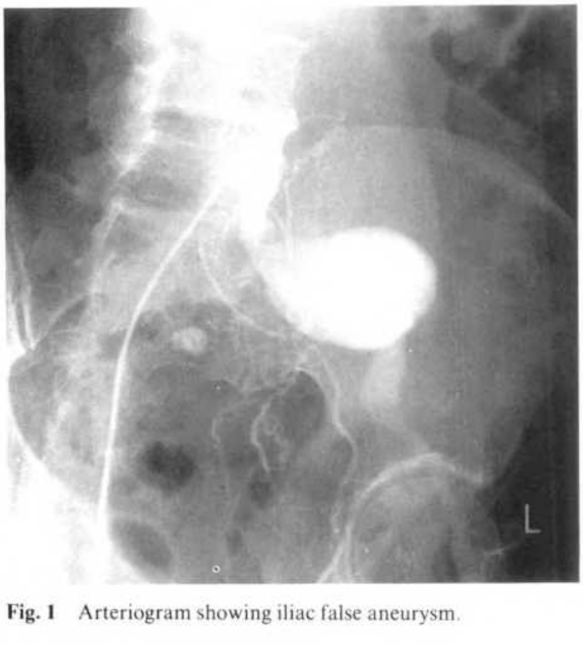

Fig. 1 Arteriogram showing iliac false aneurysm.

ureteric obstruction at L5 level. A Double-J ureteric stent (Surgitek) was passed retrogradely (Fig. 2). This was followed by deterioration in his general condition and an emergency laparotomy was performed. At operation, the false aneurysm was found to have ruptured and the ureteric stent was palpable in its wall. The aneurysm was excluded from the circulation and an aortobifemoral graft was inserted. Ureterolysis was not attempted. Six months later the patient's urinary function remains normal.

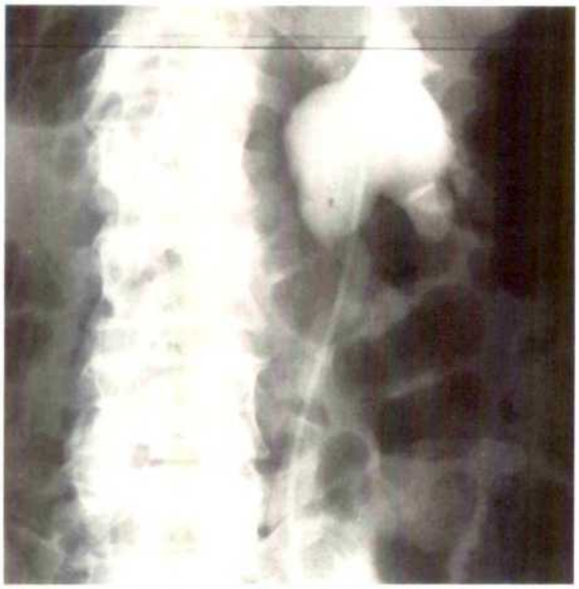

Fig. 2 Intravenous urogram showing hydronephrotic left kidney with stent *in situ*.

Comment

Anastomotic aneurysms are a recognised complication of vascular reconstruction and although rare (Treiman *et al*., 1988), may cause ureteric obstruction (Carmichael and Barnes, 1979). While a ureteric stent effects decompression and guides surgical dissection and ureterolysis, this case highlights the attendant danger of retrograde passage of a stent in the presence of ureteric obstruction due to a false aneurysm. Percutaneous nephrostomy may be more appropriate in these circumstances.

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Verrucous Carcinoma of the Penis Successfully Treated with Interferon

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Case Report

In June 1986 a 34-year-old man was admitted for circumcision because of complicated phimosis. At operation a tumour in the glans penis was found and excised. Histological diagnosis was verrucous carcinoma. Two months later a local recurrence was observed. This was excised and the tumour bed electrocoagulated. In February 1987 a second recurrence was excised and an enlarged lymph node was removed from the left groin. Histological examination of the tumour again showed verrucous carcinoma-like changes, but in the lymph node only reactive changes were observed. DNA hybridisation after amplification with the polymerase chain reaction revealed human papillomavirus (HPV) type 11 in the tumour specimen. Within 2 months of this recurrence a new, large (1 × 2 × 4 cm), fast-growing horned tumour had appeared and the glans penis was covered by numerous smaller tumours (Fig. 1). No evidence of metastases was found and the laboratory values were normal.

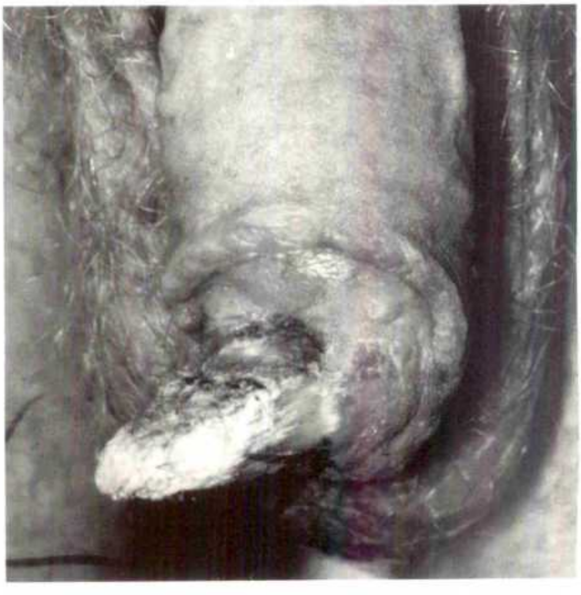

Fig. 1 Verrucous carcinoma of the penis before treatment.

In June 1987, treatment with interferon alpha (FinnferonR) was initiated and 3×10^6 units were administered daily as subcutaneous injections. The total dose between June and November 1987 was 462×10^6 units. The small changes in the penis disappeared, and the basis of the tumour horn became thinner. At this stage the horn was excised and interferon treatment was continued to the end of December 1987 (Fig. 2).

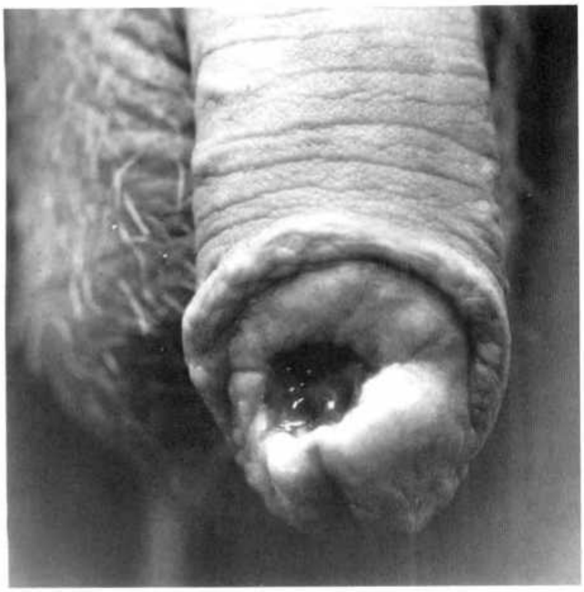

Fig. 2 Clinical status during interferon treatment 2 weeks after excision of the remaining horny tissue.

In November 1987 the patient presented with fatigue and polyuria. Laboratory tests revealed high abnormal blood levels of transaminases and glucose and diabetes requiring insulin treatment was diagnosed.

Two years after the excision the patient has no symptoms related to penile carcinoma (Fig. 3). His social and sexual life is normal and there is no evidence of local recurrence or distant metastases.

Comment

Buschke-Löwenstein tumour and verrucous carcinoma are papillomatous pre-cancerous lesions of the penis (Davies, 1965; Hanash *et al.*, 1970; Limjoco, 1974). Histologically the latter is a highly differentiated squamous cell carcinoma with a resemblance to benign condyloma. HPV infection has been proposed as an aetiological agent of penile cancer. Viral particles and viral DNA have been found in bowenoid papulosis, another type of precancerous lesion (Zelickson and Prewer, 1980), and in carcinoma of the penis (Barrasso *et al.*, 1987).

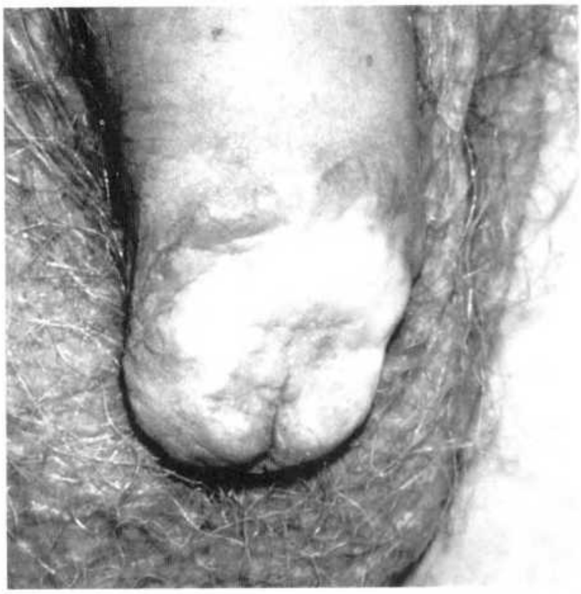

Fig. 3 Two years after combined treatment with excision and interferon.

Verrucous carcinoma is a rare tumour of the penis. It does not metastasise but recurs locally. There is no well established effective treatment and recurrences after radiotherapy and local surgical treatment are common.

Interferon treatment with some favourable results has been reported in small and benign condylomas (Pyrhönen, 1988) but its use in the treatment of verrucous carcinoma has not been described previously.

In the present case there were 3 local recurrences and amputation of the penis was considered as the treatment of choice. However, treatment with interferon combined with local excision was successful, and after 24 months' follow-up there is no evidence of recurrence.

Despite the widespread use of interferons, diabetes has not been reported as a complication and in this case we consider it to be coincidental.

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Nephrogenic Adenoma of the Ureter

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Nephrogenic adenoma has been reported in the bladder, renal pelvis and urethra, but to date there have been only 5 reports of its occurrence in the ureter (Jakse and Mikuz, 1983; Lugo *et al.*, 1983; Satodate *et al.*, 1984; Marek and Hradec, 1985; Bernado *et al.*, 1986). We present a further case of this lesion in this unusual location.

Case Report

A 37-year-old woman had a right ureterolithotomy 5 years ago because of an incarcerated calculus. This was followed a year later by another ureteric calculus with associated moderate hydronephrosis (Fig. 1). This episode resolved spontaneously. The third recurrent impacted calculus was treated by a segmental, proximal ureteric resection. Macroscopically the specimen had an obliterated lumen and microscopically it showed mucosal denudation and underlying granulation tissue extending into the muscularis, which appeared fibrotic. In the lamina propria there was an ill defined area composed of tubules surrounded by a thickened basement membrane and lined by eosinophilic granular cells (Fig. 2). The lumina of some of them had proteinaceous PAS-positive contents (Fig. 2, inset).

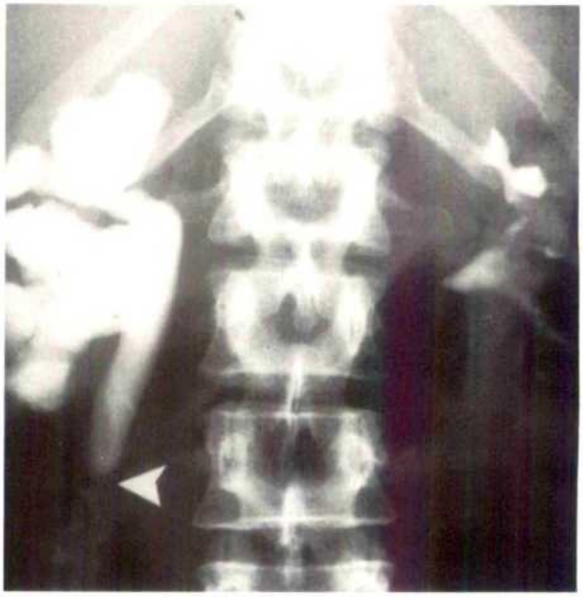

Fig. 1 Impacted calculus at the level where nephrogenic metaplasia was found, causing hydronephrosis (arrow).

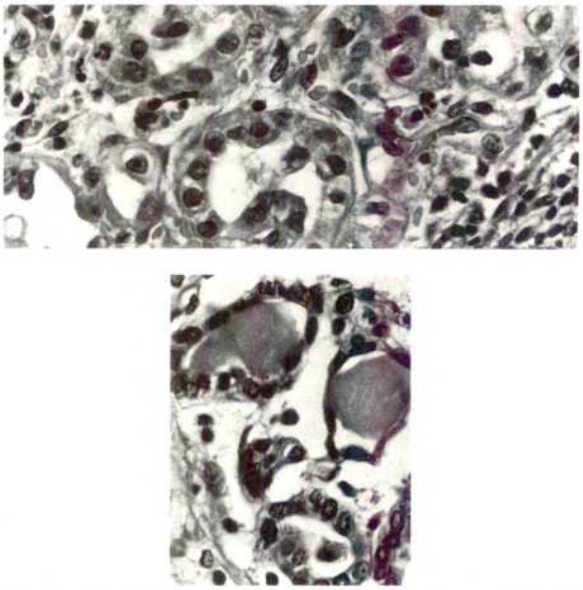

Fig. 2 Tubular structures with moderate nuclear pleomorphism. Some have proteinaceous contents (inset). (H and E × 250).

Comment

Nephrogenic adenoma is a lesion whose uncertain nature is reflected by a complex nomenclature: adenomatoid tumour, nephrogenic adenosis, nephrogenic metaplasia, *etc.* It may represent a special form of metaplastic response of the urothelium to chronic irritation; the previous cases were all related to injury such as surgical trauma, incarcerated calculi and retroperitoneal fibrosis. The present case was associated with both previous surgery and calculus. In the literature, the interval between primary insult and the development of nephrogenic adenoma ranged from 4 to 8 years. No preference for either sex or for any particular location along the ureter was noted. At presentation the patients were in the third and fourth decades, as is found with nephrogenic adenoma in other sites in the urinary tract.

The histopathological diagnosis is based on the presence of tubular formations, with hyaline contents, in the lamina propria surrounded by a basement membrane. The differential diagnoses are ureteritis cystica and clear cell adenocarcinoma of the urothelium.

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Possible Relationship of Bladder Exstrophy and Epispadias with Progestins Taken during Early Pregnancy

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The effectiveness and safety of progesterone and its derivatives in the treatment of first-trimester bleeding are still controversial. Of concern is the possible causal relationship between progestins and congenital anomalies. A cluster of infants with bladder exstrophy and epispadias born to women treated with progestins in early pregnancy is reported.

Case Reports

Of 20,650 neonates delivered in the last 5 years at the Kaplan Hospital we observed 4 male infants with epispadias, 2 of whom also had bladder exstrophy. The common denominator in all 4 cases was medroxyprogesterone-caproate given to their mothers (mean age 30.5 years, mean parity 2.3) as treatment for first-trimester threatened abortion. No other medications were given during that period and these birth defects were not associated with other congenital anomalies. Familial history was negative. Prenatal ultrasonography failed to demonstrate the exstrophic malformations. Except for first-trimester bleeding, the 4 pregnancies were uneventful and terminated by vaginal deliveries of appropriate-for-dates babies (mean birth weight 2980 g, mean gestational age 39.6 weeks). The newborn infants were referred to a tertiary centre specialising in paediatric urology.

Comment

Exstrophy of the bladder and epispadias are rare anomalies with an estimated incidence of 1:40,000–50,000 deliveries (Marshall and Muecke, 1968; Warkany, 1971). Both malformations have a common developmental origin at the 16-mm embryonic stage with a caudal position of the primordia of the genital tubercle and lack of mesodermal tissue between the cloacal plate and the belly stalk (Patten and Barry, 1952). The cluster of 4 cases represents a 10-fold increased incidence to about 1:5000 deliveries or even much higher, if only progestin-treated patients are included. An earlier report (Aarskog, 1979) suggested a possible association between hypospadias and maternal progestins but a later study (Katz *et al.*, 1985) found similar incidences of major anomalies in neonates whose mothers were treated with progestins for first-trimester bleeding when compared with those whose mothers bled but were not treated. During the study period, less than 2% of our pregnant population were treated with progestins. Thus the observed cluster, considered in relation to the rarity of epispadias and bladder exstrophy, may suggest a possible association between these urogenital anomalies and progestins given during early pregnancy.

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Ureteric Tumour in a Duplex System

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Case Report

E.G.H., a 74-year-old male Caucasian, was first seen with painless haematuria in November 1987. He had had 1 episode of haematuria 2 years previously. He was known to be polycythaemic and underwent periodic venesection. He smoked 30 to 40 cigarettes daily. There were no significant findings on examination. Urine cytology showed cells of a low grade transitional cell carcinoma and intravenous urography suggested non-function of the upper moiety of a left duplex system. This was confirmed on ultrasound and CT scan (Fig. 1). At cystoscopy a single left ureteric orifice was observed and a left retrograde pyelogram demonstrated only the lower moiety. Antegrade pylelography was not done because of the risk of spilling tumour cells. Exploration carried out through an extended loin incision revealed the upper moiety of a bifid kidney drained by a tortuous dilated ureter which was obstructed by a tumour proximal to its junction with the other ureter about 5 cm before its entry into the bladder. An upper nephroureterectomy was performed. Histology revealed a papillary invasive transitional cell carcinoma (G2pT2); the resection margin was free of tumour. The upper moiety showed papillary necrosis but no pyelonephritic changes.

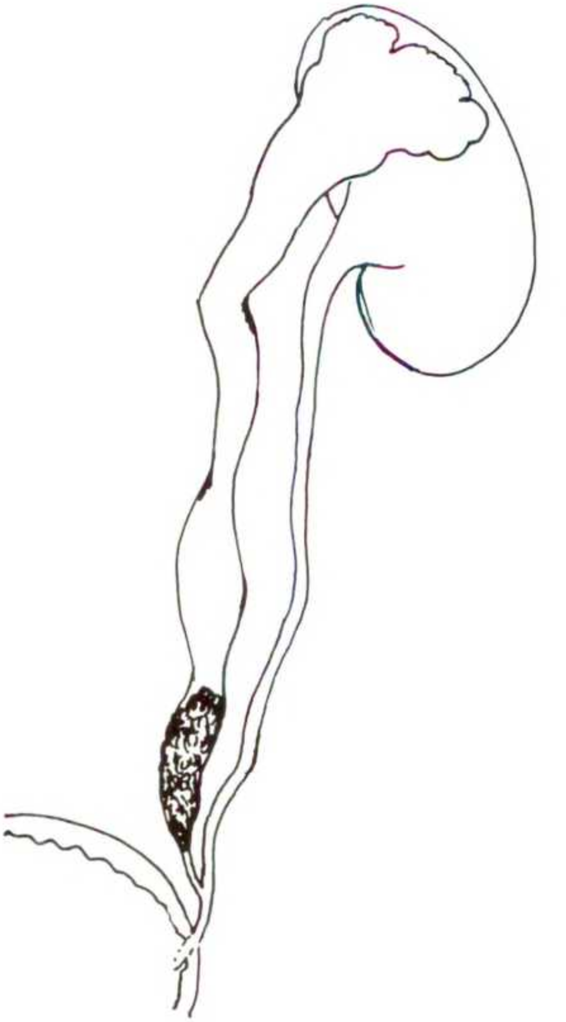

Fig. 1 (A) CT scan showing upper moiety with thin rind of cortex (arrowed). (B) The non-opacifying ureter draining it is anterior to the orthotopic ureter (arrowed).

Comment

Tumour in a duplex system is very uncommon and in the past decade only 1 such case has been reported (Tudor and Clear, 1986). Despite our suspicions based on IVU and ultrasound, retrograde pyelography using a standard ureteric catheter did not outline the ureter draining the upper moiety because it was obstructed (Hartman and Hodson, 1969). A plug-type ureteric catheter (*e.g.* Rutner wedge or Chevassu) may have defined the upper ureter. Antegrade pyelography would have demonstrated the lesion (Allison, 1986) but we considered that the risk of introducing infection or spilling tumour cells was unacceptable.

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Bladder Exstrophy Complicated by Adenocarcinoma

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Exstrophy of the urinary bladder is an uncommon congenital deformity occurring in every 30,000 to 40,000 live births. A greater risk of developing carcinoma has been well documented, especially in patients surviving to adulthood. Since the first case was reported by Bergenhem in 1895 (Goyann, 1951), about 80 cases have been added to the literature (Witters and Da, 1987). We report a 52-year-old man with adenocarcinoma of the bladder and untreated exstrophy.

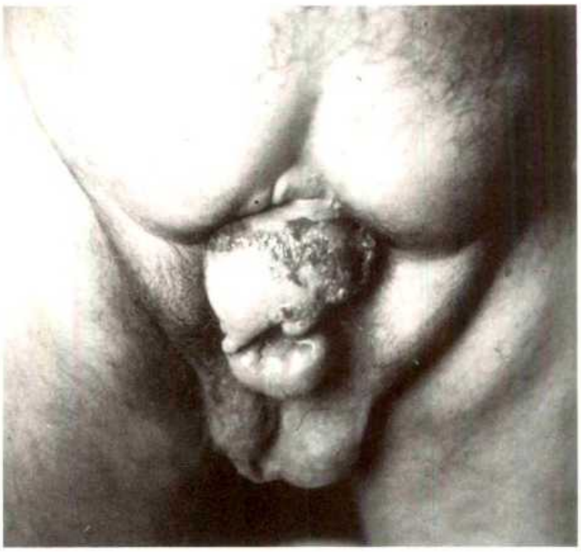

Fig. Anterior view of bladder exstrophy.

Case Report

A 52-year-old man was admitted with bladder exstrophy and complete epispadias. He reported that shortly after his birth his mother took him to hospital, where exstrophy was diagnosed, but for some unknown reason he was not operated upon. There was no history of infection and his general condition had been excellent. For some months before his admission he had been aware of a complete change in the appearance of his bladder, which became hyperaemic and granulomatous (Fig.). An IVU was normal but demonstrated separation of the pubic symphysis and biopsies of the bladder showed an adenocarcinoma.

The patient was operated upon and total cystectomy was performed with ureterosigmoidostomy. The postoperative period was complicated by a urinary leak that stopped spontaneously. Pathological examination of the bladder showed an adenocarcinoma stage pT2. One year later the patient is well.

Comment

Since the first reported case of malignant degeneration in bladder exstrophy in 1895 (Goyann, 1951), at least 82 cases have been reported in the literature. Although primary adenocarcinoma of the bladder accounts for approximately 1% of epithelial bladder neoplasms, an adenocarcinoma was found in 70 of the reported cases (Witters and Da, 1987). The pathogenic mechanism giving rise to adenocarcinoma in bladder exstrophy could be either metaplasia or ectopia (the latter propably due to rectal epithelium misplaced during division of the cloaca), or proliferation of an uncommitted reserve of stem cells.

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British Journal of Urology (1991), **68**, 108–109

Points of Technique

Use of a Straw for Suprapubic Stab Puncture—an Alternative Method

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The technique of suprapubic stab puncture has been used in 80 cases. The use of a straw to introduce a large size Foley catheter is considerably cheaper than using a sophisticated peel-away sheath introducer.

Using a straw as a third (outer) sheath over the commonly used Reuter trocar and cannula provides all of the features of a peel-away sheath introducer and is a cost-effective alternative method.

Technique

The instruments include a Reuter trocar and cannula No. 16F (Storz) and a straw (easily available in restaurants, etc). The plastic straw is cut into 2 equal halves. Each slides easily over the cannula and the length is adequate (slightly shorter than the cannula). The instruments are sterilised with Cidex solution for 20 to 30 min. The procedure is carried out under local anaesthesia. A small stab incision is made. The trocar and cannula with the half straw are slid over as the outermost sheath is introduced into the bladder. The trocar and cannula are withdrawn. A gush of urine through the straw confirms entry. A 16F Foley catheter is inserted through the straw. As the catheter starts draining urine the balloon is inflated. The straw is withdrawn from the wound, cut longitudinally over the catheter, removed and discarded.

Requests for reprints to: A. G. Tilak, "Asavari" C-16, 214, S.V.S. Marg, Mahim, Bombay–400 016, India.

Transbrachial Approach in Spermatic Phlebography

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Of 131 patients undergoing phlebography, a new percutaneous transbrachial approach was used in 67. Both catheterisation and embolisation of the right and left internal spermatic veins (ISV) were easier than with the transfemoral approach, particularly on the right side as a result of the craniocaudal progression of the catheter. This new technique is recommended for the management not

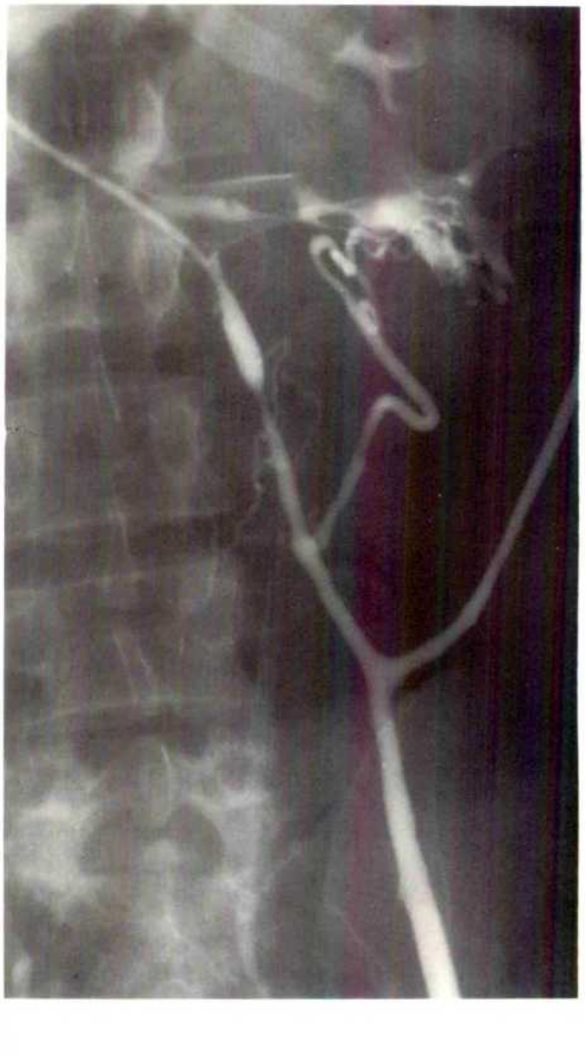

Fig. 1 Left spermatic vein. Selective catheterisation through the left transbrachial approach. There is venous duplication with a separate reflux into the right renal vein.

only of right-sided or bilateral varicoceles, but also left-sided ones.

The transfemoral approach is usually employed for catheterisation, retrograde phlebography and embolisation of the internal spermatic veins. With this technique the catheter tip in the ISV travels in the opposite direction to that taken in the inferior vena cava (IVC). This does not facilitate catheterisation manoeuvres in the ISV, especially on the right side (Formanek *et al.*, 1981; Morag *et al.*, 1984).

The percutaneous transjugular approach allows cranio-caudal progression of the catheter and catheterisation of both the left and the right ISV is much easier. However, this approach is less well tolerated by the patient and may give rise to complications, *e.g.* pneumothorax.

As a result of these problems we have devised a new percutaneous brachial approach.

Technique

We use a disposable, pre-shaped, multi-purpose 5 or 6 F catheter, 100 cm long and J-shaped, with a guidewire. For transbrachial access, a 16 gauge cannula is inserted into the basilic or cephalic vein. The catheter is pushed through the axillary vein, the superior vena cava, the right atrium, the inferior vena cava and the right or left ISV (Figs 1 and 2).

The injection of contrast medium and the technique for the transfemoral approach are as described by Belgrano *et al.* (1984).

Between 1985 and 1988, 131 patients with varicocele (age range 17–40 years) underwent phlebography by either the transfemoral or the transbrachial route (Table 1). All patients were subjected to urological examination, Doppler test and seminal fluid analysis (Table 2). No statistical difference was found between the 2 techniques (Student's t test) even when the fluoroscopy time was reduced with the transbrachial approach. There were no side effects.

Table 1 Procedures

Phlebography	*Left*	*Right*
Transfemoral access	70	11
Transbrachial access	59	8
Embolisation	38	4

Table 2 Results

	Transbrachial	*Transfemoral*
Selective catheterisation failure	4.4%	7.8%
Average fluoroscopy performed to visualise ISV	1′30″	2′″*
Average time for fluoroscopy necessary for embolisation	4′	8′*

*P not statistically significant.

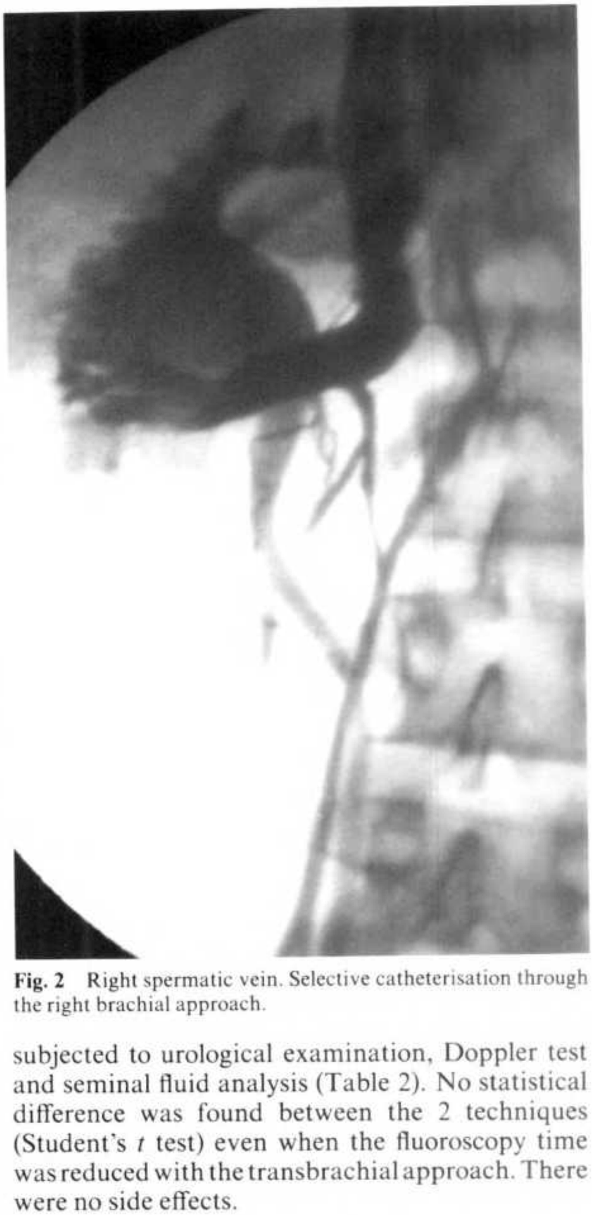

Fig. 2 Right spermatic vein. Selective catheterisation through the right brachial approach.

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Requests for reprints to: F. Di Silverio, Department of Urology, University of Rome "La Sapienza", Policlinico Umberto I, Viale del Policlinico, 00161 Rome, Italy.

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Notices

The Surgitek Prize

The Prize consists of a fully sponsored visit to the American Urological Association Annual Five-day Meeting, together with a tour of Surgitek's manufacturing facility in Racine, Wisconsin. It is open to trainees in urology and consultants who are within 5 years of first appointment. Entrants should submit a written paper, which may be on any subject, but must be unpublished, and must not have been submitted previously for the Surgitek Prize, or other prizes. The winning entry will be the one which is considered to be "The most significant contribution to urology".

Entries will be judged by three members of BAUS Council nominated at the October meeting of Council. Papers should be submitted in triplicate to the Honorary Secretary by 1 January each year.

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Diary

1991

August 21–23	Edinburgh Urological Festival. Contact: Urological Festival Secretary, Department of Surgery/Urology, Western General Hospital, Crewe Rd, Edinburgh EH4 2XU.
August 22–24	Nordic Association for Andrology. Nordic Symposium on Epididymis and Annual Meeting, Sønderborg, Denmark. Contact: L. Linnet, Department of Surgery K, Sønderborg Hospital, DK-6400 Sønderborg, Denmark.
August 25–31	First Urology Summer Forum, Oosterbeek. Contact: Secretariat Organization, PO Box 226, 3830 AE LEUSDEN, The Netherlands.
September 1–6	6th World Congress in Ultrasound, Copenhagen. Contact: Spadile Congress Service, Sommervej 3, DK-3100 Hornbaek, Denmark. Tel: 45 2 20 24 96.
September 4–7	Twenty-first Congress of the International Continence Society. Budapest, Hungary. Contact A. Tankó, Üllõi ut 78/b, Department of Urology, Semmelweis Medical School, H-1082 Budapest, Hungary. Tel: (36) 1 1139 016.
September 16–19	Second Beijing International Symposium on Recent Advances in Urology, Beijing, China. Contact: Gu Fang-liu, Institute of Urology, Beijing Medical University, 1 Da Hong Luo Chang, West District, Beijing 100034, China.
September 26–27	Annual Paediatric Urology Course, Cambridge. Contact: Mr R. H. Whitaker, Department of Urology, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.
October 3–5	Annual Meeting of Swiss Society of Urology, Geneva, Switzerland. Contact: Prof. Dr D. Hauri, Urologische Klinik, Universitätsspital, CH-8091 Zürich, Switzerland.
October 4–5	Autumn Meeting, Royal Surrey County Hospital, Guildford. Contact: BAUS Office.
October 9–12	1st International Congress, Dutch Urological Association (NVU), Rotterdam. Contact: NVU/PACIOU Congress Secretariat, Department of Urology, Erasmus University Rotterdam/Academic Hospital Dijkzigt, P.O. Box 1738, 3000 DR Rotterdam. The Netherlands.
October 10–12	International Continence Society, 21st Annual Meeting, Hannover. Contact: Guus Kramer, Chairman ICS, Department of Urology, Hannover Medical School, P.O. Box 610180, 3000 Hannover 61, Germany.
October 18–19	Surgical Treatment of Prostatic Cancer: Comparison of Techniques. Milan, Italy. Contact: Dr F. Gaboardi, Divisione di Urologia, Ospedale Fatebenefratelli ed Oftalmico, C.so Porta Nuova 23, 20121 Milan, Italy. Tel. 0039-2-636443.
October 20–November 4	Royal College of Surgeons of England Joint Meetings in Pakistan and India. Contact: Craig Duncan, Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London, WC2A 3PN.

November 15–16	Third Biennial Asia-Pacific Meeting on Impotence, Taipei, Taiwan, R.O.C. Contact: Third Biennial Asia-Pacific Meeting on Impotence, c/o Taiwan Conference Management Co. Ltd, P.O. Box 68–439, 6F–3, 102 Chung Shan N. Road, Sec. 2, Taipei, Taiwan, R.O.C.
November 22–23	International Symposium on Minimally Invasive Therapy of Pelviureteric Junction Obstruction, Nuneaton. Contact: Mr P. Shridhar, Department of Urology, George Eliot Hospital, Nuneaton CV10 7DJ.
1992	
January 10	Final date for submission of abstracts for the 1992 BAUS Annual Meeting.
March 8–13	19th Biennial Congress of the Urological Association of South Africa, Sun City, South Africa. Contact: Dr I. Lissoos, 1 Esselen Towers, Esselen Street, Hillbrow, 2001, South Africa.
March 19–21	Eleventh International Symposium of Operative Andrology. Istanbul, Turkey. Contact: Dr A. Kelâmi, Brahmsstrasse 32, D-1000 Berlin 45, Germany.
April 9–11	6th International Urological Symposium. Girne, North Cyprus. Contact: Dr A. Kelâmi, Brahmsstrasse 32, D-1000 Berlin 45, Germany.
May 6–8	8th International Symposium on Radionuclides in Nephrourology, The Grosvenor Hotel, Chester, England. Contact: Mr P H O'Reilly, Department of Urology, Stepping Hill Hospital, Stockport, SK2 7JE.
May 10–14	American Urological Association, Washington Convention Centre, Grand Hyatt, Washington DC.
May 24–28	Inaugural Meeting of Pan African Urological Surgeons' Association, Harare, Zimbabwe. Contact: Mr A. P. Danso, Department of Surgery, University of Zimbabwe Medical School, P.O. Box A 178, Avondale, Harare, Zimbabwe.
June 10–12	Continent Urinary Reconstruction. First International Meeting. Lund, Sweden. Contact: Dr Wiking Månsson, Department of Urology, University Hospital, S-22185 Lund, Sweden.
June 21–26	BAUS Annual Meeting, Bournemouth International Centre, Bournemouth. Contact: BAUS Office.
June 22–25	Canadian Urological Association Annual Meeting, Winnipeg. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.
July 22–25	European Association of Urology, 10th Congress, Genoa. Contact: Conference Secretariat, Top Congress—P.R., Piazza Galeazzo Alessi 2/1, 16128 Genoa, Italy.
August 24–27	Third European Symposium on Uroradiology. Herlev, Denmark. Contact Dr H. S. Thomsen, Department of Diagnostic Radiology 54E2, Herlev Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark.

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Wright, F. S. and Howards, S. S. (1981). Obstructive injury. In *The Kidney*, ed. Bremner, B. M. and Rector, F. C. Second edition. Volume II Chapter 38, pp. 2009–2044. Philadelphia: Saunders.

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REVIEW

The Current Status of Lithotripsy

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Department of Urology, St Bartholomew's Hospital, London

Technological improvements in lithotriptor design and greater clinical experience using shock waves have led to a diversification of treatment indications for lithotripsy. These, and the limitations and complications of the treatment, are outlined in this update of a rapidly changing subject.

Seldom has the introduction of a new medical technology revolutionised medical practice more than lithotripsy has changed the approach to urinary tract calculus disease. Since February 1980 and the first clinical application of electrically generated, focused shock waves on a human kidney (Chaussy *et al.*, 1980), lithotripsy has become the preferred method of treatment for the majority of renal calculi. The efficacy of this treatment was apparent from early reports and this has led to its adoption worldwide; over 2,000,000 treatments have now been performed on more than 1100 machines. This success has produced rapid technical advances in machine design, with at least 15 models now available commercially, and a diversification of indications for treatment. However, this speed of change carries with it the possible risks of obscuring the proper role and potential complications of this form of treatment. It is because of these rapid changes that we review the current position of lithotripsy.

Technical Changes

Electrohydraulic shock wave technology was first adapted for use in stone destruction in Russia in the 1950s (Ison, 1987). This internal electrohydraulic lithotripsy (EHL) required direct contact with the stone, and at that time access was restricted to bladder stones. The technique enabled bladder calculi to be fragmented effectively but carried with it the hazards of tissue damage, both from the energy source and from the means of gaining access to the stone. Research into the development of externally generated shock waves to distintegrate stones involved the study of methods of wave generation, focusing, and transmission through tissue with minimal energy loss and tissue damage. This research led to the production of the first commercial lithotriptor by Dornier in 1980. Since then "second" and "third generation" machines have become available which vary in the generation and mode of delivery of the shock wave to the stone, and the method of stone localisation.

Shock wave generation involves the conversion of one form of energy into the acoustic form. The spark-gap principle of shock wave production was incorporated into the original and most subsequent Dornier lithotriptors. A high voltage is discharged between 2 electrodes under water and the resulting plasma creates a spherically expanding shock wave which is reflected in a hemi-ellipsoid chamber to a forward second focus point, F2 (Ison, 1987). Other machines use different methods of shock wave generation, and those that have achieved commercial success are the piezoelectric and electromagnetic sources. When an external electric field is applied across a piezoelectric crystal the change in external dimensions of the crystal produces a pressure wave. A mosaic of about 3000 crystals is placed in a curved generator dish, and the individual waves summate to produce a forward focus of waves. Electromagnetic shock wave generation involves the intermittent repulsion of a flexible metal membrane and produces a pressure wave which can be focused by an acoustic lens. This variety of techniques in shock wave generation and focusing has produced machines with differing specifications. The first generation Dornier HM3, the "gold standard" against which later machines were compared, had a powerful 80 nF generator

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but a large focus size which necessitated general anaesthesia for treatment. The efficacy of this "gold standard" has subsequently been surpassed.

The second generation lithotriptors have a wider range of functions which can be performed without the need for general anaesthesia or a waterbath and with equal efficiency of stone fragmentation. The piezoelectric systems have a less powerful generator and a larger dish aperture which results in a lower energy density/cm^2 of skin and a painless zone of shock entry into the body. The overall smaller focus size and lower focal point energy dissipation require more treatment sessions for complete stone clearance. The latest generation of machines produce a high focal pressure with a wide surface aperture to provide maximal stone fragmentation without the need for general anaesthesia (Tailly, 1990) or immersion in water. They are also equipped with both X-ray and ultrasound imaging modalities to provide accurate stone location throughout the urinary tract. Ultrasound devices provide accurate, real-time, cost-effective localisation without X-ray exposure, and are more effective for the localisation of radiolucent urinary calculi and gallstones. Technical improvements in ultrasound equipment have facilitated interpretation. Ultrasound is also an imaging modality which has become increasingly familiar to the urologist. The majority of ureteric and common bile duct stones, however, require fluoroscopy and so there is a need for comprehensive multi-functional imaging.

The range of machines now available with different technical specifications and imaging modalities allows a choice to suit any particular range of applications (Table).

Current Clinical Indications and Results

The indications for extracorporeal shock wave lithotripsy (ESWL) established in the early clinical trials were for solitary, radio-opaque calculi in the renal calices or pelvis and measuring less than 20 mm in diameter. The efficacy, safety and reliability of the method have widened the range of indications to include most urinary stones and a number of biliary and salivary calculi. Improved imaging quality has allowed visualisation of most calculi throughout the urinary tract. This, combined with endoscopic procedures that prevent or treat any complications that may develop, means that nearly all urinary calculi can now be treated with ESWL, and 75% of these as monotherapy. The remainder require an auxiliary procedure to facilitate ESWL but open surgery is indicated in less than 3% (Fig. 1). Endourological techniques are an essential adjunct for successful ESWL; they have broadened the indications for ESWL and in many cases permitted the resolution of the complications (Eisenberger *et al.*, 1985).

The results of ESWL are traditionally reported as the incidence of stone clearance achieved at various intervals from 1 week to 3 months following treatment. The standardisation of reporting results and all terminology relating to ESWL has been reported by Tolley *et al.* (1991). Until this is widely accepted, comparison of results between centres cannot be made as treatment philosophies, as well as lithotriptor specifications, vary.

Renal Stones

During the early years of lithotripsy the Munich group reported that 99% of stones fragmented and that 90% of patients were stone-free at 3 months (Chaussy *et al.*, 1980). Despite the use of a variety of lithotriptors the results for these simple stones are remarkably consistent, although the number of treatments required to achieve clearance is a reflection of the lithotriptor used. Results from all centres have subsequently confirmed that clearance rates depend on the size and position of the stone. As the stone burden increases, the overall stone-free rates diminish. Similarly, the shape of the renal collecting system and the architecture of the dependent calices determine whether satisfactory fragmentation and clearance can occur. Stones in calices with narrow infundibula will not provide results comparable to those achieved with renal pelvic stones. These determinants of stone clearance are especially relevant when managing larger renal calculi. These may require multiple treatment sessions or adjunctive procedures and so results should always be compared with those achievable by percutaneous nephrolithotomy (PCNL). This is especially relevant to staghorn calculi. A staghorn is defined as a solitary calculus with a pelvic, infundibular and caliceal component and may be partial, when 2 calices or less are involved, or complete, when the collecting system is filled. Staghorn calculi represent a significant challenge to the urologist. Interventional therapy is required if renal deterioration is to be prevented, but the treatment itself can cause renal damage. This was recognised before the advent of ESWL, with surgical techniques aimed at renal conservation with percutaneous nephrolithotomy providing minimal invasion and maximal efficacy (Segura *et al.*, 1985). ESWL as a non-invasive procedure has the

Table Lithotriptor Specifications

Lithotriptor	*Shock wave generation*	*Coupling*	*Localisation*	*Anaesthesia*
Dornier HM3	Spark gap	Water bath	X-ray	General/epidural
Dornier HM4	Spark gap	Water cushion	X-ray	Sedoanalgesia
Dornier MPL 9000	Spark gap	Water cushion	X-ray or U/S	No, sedoanalgesia
Dornier Compact	Electromagnetic	Water cushion	U/S	No, sedoanalgesia
Direx	Spark gap	Water cushion	X-ray	Sedoanalgesia
EDAP	Piezoelectric	Water cushion	U/S	No, sedoanalgesia
Medstone	Spark gap	Water cushion	X-ray	Sedoanalgesia
Siemens Lithostar	Electromagnetic	Water cushion	X-ray	No, sedoanalgesia
Technomed Sonolith	Spark gap	Partial water bath	X-ray or U/S	No, sedoanalgesia
Wolf 2300	Piezoelectric	Partial water bath	U/S	No

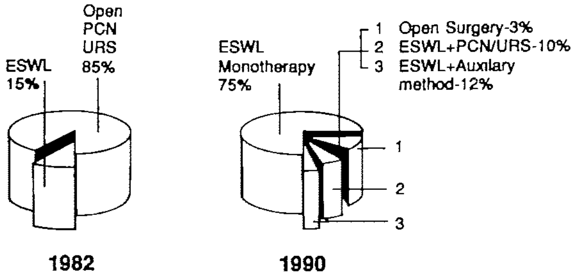

Fig. 1 Changing role of lithotripsy between 1982 and 1990 in the treatment of urinary tract stones.

lowest morbidity of the treatment options and can be used either as monotherapy or in conjunction with auxiliary endourological procedures in order to minimise or treat ensuing complications.

Unselected patients treated with monotherapy ESWL have a high incidence of ureteric obstruction and urosepsis and a relatively low stone-free rate of approximately 45% (Gleeson and Griffith, 1989). The stone-free rate is comparable to that following PCNL for smaller stones but diminishes as the stone burden increases. The outcome of this monotherapy, as discussed above, depends on stone burden, renal anatomy and stone composition. Based on these criteria, predictions can be made as to which calculi will need auxiliary procedures in the form of debulking either prior to or following ESWL, or adjunctive ureteric stenting to improve the efficacy of treatment and diminish the complication rate. The prophylactic retrograde insertion of a ureteric stent prevents ureteric obstruction from a "Steinstrasse" and shortens the interval between consequent ESWL sessions (Libby *et al.*, 1988). In this way, large staghorn calculi with multiple branches can be managed by staged ESWL monotherapy (Pode *et al.*, 1988). However, the low stone clearance rate, high incidence of complications and rehospitalisation, and the need for multiple therapy sessions, favour a combined approach of PCNL and ESWL (Fuchs and Chaussy, 1987).

ESWL therapy requires easy discharge of stone debris. In the presence of renal pelvic dilatation or any urodynamic alteration of the upper urinary tract, inadequate drainage will inhibit this discharge and necessitate percutaneous extraction.

The composition of the stone can also determine or influence the treatment selected for a particular stone. Calcium monohydrate and cystine stones are particularly hard and resistant to ESWL. Infected staghorns, which are composed of struvite, are relatively soft but unless all fragments are eradicated the stone may rapidly recur. The infecting bacteria are incorporated into the matrix of the staghorn calculus and are released on stone fragmentation to reinfect the urine. Thus the aim must be maximal stone clearance and this usually involves a combination of PCNL and ESWL in order to minimise recurrence. Spirnak (1988) reported improved stone clearance for struvite calculi using renal irrigation with hemiacidrin to flush out and dissolve the small residual fragments, but the long period of nephrostomy irrigation required for this has hindered its widespread use.

The management protocol for staghorn calculi should be individualised, depending on the variables of stone burden, renal function, intrarenal anatomy, the presence of infection, the presence of obstruction and the expectations of the patient. It should be remembered that patients with complex calculus disease with anatomical or physiological abnormalities may be best served by open anatrophic nephrolithotomy, from which excellent results can still be obtained (Assimos *et al.*, 1989).

Ureteric Stones

The management of symptomatic ureteric stones has progressed from open ureterolithotomy to basket extraction and antegrade or ureteroscopic removal to non-invasive ESWL. Early experience of ESWL with upper ureteric stones showed that they were more resistant to fragmentation than pelvic or caliceal calculi and that successful treatment depended not only on size, position and composition but mostly on the degree of impaction of the stone. As clinical experience of ESWL has expanded and the second generation lithotriptors have become available, upper and mid-ureteric stones have been successfully treated. The difficulties associated with these calculi are: (1) the proximity of the ureter to the vertebral column and the potential for causing pain, (2) the more anterior position of the ureter compared to the kidney, which takes the stone further away from the therapy head, and (3) the inability of fragments to separate from the stone bulk during treatment.

These difficulties provoke the need for more shock waves, a higher generator voltage and more re-treatments in order to achieve fragmentation and stone clearance. As a consequence, primary stone manipulation into the renal pelvis, the "push-bang" technique (Coptcoat *et al.*, 1987) and bypassing the stone with a double pigtail stent were advocated to facilitate ESWL. The placement of a double pigtail stent alongside a calculus was reported by Dretler (1986) to improve the likelihood of successful *in situ* treatment. However, although it may improve imaging and visualisation of the stone, this experience has not been corroborated and subsequent studies do not suggest an overall increased rate of stone clearance. This may be related to the observation that double pigtail stents inhibit ureteric peristalsis and thus the passage of stone fragments (Ramsay *et al.*, 1985).

Retrograde stone manipulation of upper and mid-ureteric stones into the renal pelvis results in stone disintegration in 95% of cases (Lingeman *et al.*, 1987). However, 20% of these stones cannot be mobilised by stents or ureterorenoscopy (URS) and the invasive nature of these procedures should be considered potentially deleterious. Even in the most skilled hands, perforation and stricture can occur in up to 5% of ureteroscopies. As a result, despite the need for more shock waves and a higher re-treatment rate, *in situ* ESWL is the preferred management in many centres.

Stone manipulation is, however, required more often for use in conjunction with lithotriptors that use ultrasound as the sole imaging modality. Using ultrasound scanning it is rarely possible to see ureteric stones unless they are imaged either using the kidney or the full bladder as an "acoustic window", or unless the ureter is dilated. This excludes all but the uppermost and the most distal intramural ureteric calculi. Calculi between these sites will require manipulation which may be performed on a multifunctional lithotripsy table.

Until recently, middle and lower third ureteric calculi were regarded as unsuitable for *in situ* ESWL owing to disappointing results. This was due to the difficulty of imaging stones below the iliac crest and the attenuation of the shock wave from the bony pelvis. However, modified patient positioning techniques have allowed access for treatment either through the gluteal region with the patient flat and supine, through the perineum with the patient in the sitting position, or with the patient lying prone. Excellent results have been achieved in a large series which reported 82% of 133 distal calculi being disintegrated in 1 treatment session (Miller and Hautmann, 1987). These results compare favourably with the results of ureteroscopy and also with lithotripsy of upper ureteric calculi.

In situ ESWL is therefore safe, non-invasive and may be considered the first-line treatment for all ureteric calculi with a suitable lithotriptor, resulting in total stone clearance in 75% of patients (Fig. 2).

Complications

Treatment with ESWL produces renal changes comparable to those following renal trauma. The short-term effects of these changes are well established and well tolerated, but before full acceptance

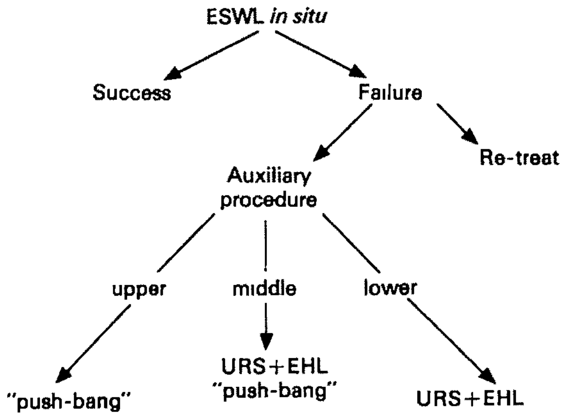

Fig. 2 Suggested management of ureteric stones.

of this new technology can be made, long-term effects need to be evaluated. The potential complications include loss of renal function, hypertension and stone recurrence. The diversification of treatment indications has resulted in patients receiving a greater number of shocks at a higher voltage, without safety limits being established.

Short-term effects

Haematuria is the most common immediate effect and is related to renal parenchymal damage rather than the passage of stone fragments. However, these fragments may cause ureteric obstruction, depending on the particle size and the initial stone burden. The incidence of "Steinstrasse" requiring endourological intervention is related to the fragment size and the treatment philosophy of the centre concerned. Urosepsis is a recognised complication of treatment of patients with either infective stones or positive urine cultures and prophylactic antibiotics are mandatory. However, the low incidence of infection occurring after treatment of other stones has led to many centres using a selective policy for such prophylaxis.

Recent attention has focused on the effects of shock waves on renal morphology and subsequent renal function. Renal parenchymal changes are reflected in increases in serum and urinary values of enzymes, and the demonstration of subcapsular and intraparenchymal haemorrhage. Animal studies have shown that renal morphological changes are dose-dependent and transient, and long-term damage occurs only when the shock wave dose is vastly exceeded (Newman *et al.*, 1987). The immediate changes include perirenal and intraparenchymal haemorrhage and interstitial oedema, with the small renal parenchymal veins being the most susceptible to damage. Similar changes are seen in human kidneys, the incidence of which appears to depend on the sensitivity of the imaging modality used. Ultrasound scanning by Chaussy and Schmidt (1984) detected subcapsular haematomas in 0.6% of almost 1000 patients examined after ESWL. Rubin *et al.* (1987) found an incidence of 15% using computed tomography (CT) scanning and Kaude *et al.* (1985) reported 24% using magnetic resonance imaging (MRI), with a total of 63% of kidneys having some identifiable abnormality. Raised urinary and serum laboratory values of various intracellular enzymes indicate trauma to renal parenchyma, liver and skeletal muscle. These also were dose-dependent and transient, returning to normal within 7 days (Haupt *et al.*, 1989). The significance of these morphological and biochemical changes in terms of renal function is uncertain. Kaude *et al.* (1985) showed a statistically significant reduction (5%) in effective renal plasma flow (ERPF), and in a study by Bomanji *et al.* (1987) the glomerular filtration rate (GFR) was significantly reduced by 8% in the treated kidney. The GFR was measured by radionuclide scanning and was also noted to be mildly reduced in the contralateral untreated kidney, though these effects were only transient. The effects on the treated kidney may not be simply transient and have been found to persist in up to 24% of kidneys when measured 17 to 21 months after treatment (Williams *et al.*, 1988).

The exact mechanism of these changes is not certain but it has been speculated that the "cavitation" effect behind a passing wave may be the cause. The different methods of shock wave production now available may mean that some machines are less damaging than others and there is some evidence that piezoelectric generators produce no significant impairment of renal function as measured by radionuclide scanning (Daniel and Burns, 1990).

Significant renal haemorrhage and minor renal impairment can occur after ESWL and this should be considered when treating unilateral kidney stones or patients with asymptomatic stones.

Long-term complications

The potential long-term adverse effects of ESWL that are currently being addressed are an increased rate of new stone formation, a decrease in renal function and an increase in systemic blood pressure. Long-term follow-up studies to define persistent or recurrent stone disease are scarce, with the incidence of stone-free kidneys up to 21 months after treatment varying from 50 to 84% (Miles *et al.*, 1987). However, in these studies less than 5% of patients had developed new or recurrent stone growth, which is less than the expected incidence in patients with untreated urolithiasis.

The observations of renal trauma and renal impairment immediately after ESWL led to retrospective studies aimed at establishing whether permanent renal damage and/or hypertension were long-term sequelae. The mechanism of renal impairment and hypertension is thought to be similar to that observed after renal trauma, i.e. the Page kidney. Perirenal haemorrhage is followed by organisation and fibrosis with compression of the renal parenchyma resulting in an alteration in renal haemodynamics. This mechanism is purely hypothetical and it may be multi-factorial, with other pathologies such as renal artery stenosis being contributory.

In 1987 Lingeman and Kulb reported an 8% incidence of hypertension in a population of 900 patients treated with ESWL, followed up for a mean of 1.5 years. A remarkably similar incidence was reported by Williams *et al.* (1988), although the difficulties in providing adequate control groups were noted by the authors. A subsequent study by Lingeman *et al.* (1990) found no rise in the annual incidence of hypertension following ESWL when compared with a control group of stone formers. They did, however, find a statistically significant rise in the diastolic blood pressure after ESWL compared with the control group. The case remains unproven and the need for a prospective, multicentre controlled study with adequate follow-up is expressed by all authors.

Gallstones

The first successful non-invasive shock wave lithotripsy of gallstones, performed in 1985 (Sauerbruch *et al.*, 1986), has stimulated extensive clinical trials of biliary ESWL and also the development of further minimally invasive treatment modalities for gallstones. The success of urinary tract ESWL cannot, however, be directly extrapolated to the treatment of biliary stones owing to anatomical and physiological features of the gallbladder and the composition of the stones. Approximately 30% of patients referred for biliary stone treatment in the initial trials fulfilled the selection criteria, though subsequent studies have inclusion rates that vary from less than 10% to 40% of symptomatic patients. Current pre-conditions for lithotripsy of symptomatic gallstones are:

1. Radiolucent calculi.
2. Functioning gallbladder.
3. Maximal size 30 mm.
4. Up to 30% of gallbladder volume filled with stones.
5. Good ultrasound localisation.

Contraindications are:

1. Obstructed biliary tree.
2. Pregnancy.
3. Abdominal aortic aneurysm.
4. Hydatid near gallbladder.
5. Coagulopathy.

Treatment can be performed without anaesthesia, with ultrasound guidance for gallbladder stones and X-ray guidance for the infrequent common bile duct stone. Short-term complications include biliary colic (29%), which can last for up to 1 month, cutaneous petechiae (14%), haematuria (7%), pancreatitis (1%) together with the known side effects of the litholytic agents.

Within the selected treatment groups successful stone fragmentation and reduction in stone volume have been achieved in approximately 99%. However, stone clearance is not so easily achieved. Almost 55% of patients treated are stone-free after 6 months and approximately 80% at 12 months, with the greatest stone clearance being achieved in patients with a solitary stone (70% and 90% at the same intervals). The corresponding values reported for litholytic therapy alone are 18 and 38% respectively (Sackmann *et al.*, 1988).

Thus ESWL provides safe and effective therapy for selected patients with radiolucent gallstones, especially those with solitary stones. The treatment modality must, however, be kept in perspective in terms of other treatment options that are available. Gallbladder and biliary anatomy and physiology do not favour the concept of lithotripsy and the lithogenic factors that initiated stone formation may remain after the disappearance of the stones. Recurrence rates have not been clearly established, though evidence suggests that the risk is low if no stones are found in the 2 years following treatment.

Percutaneous cholecystolithotomy (PCCL) evolved from the expected need to decompress an obstructed system following ESWL, and has developed into a separate treatment modality (Chiverton, 1990). The technique of laparoscopic cholecystectomy is now popular in the USA, where the majority of patients are discharged from hospital within 24 h and return to work within 7 days following this minimally invasive procedure (Reddick, personal communication).

The role of ESWL in the treatment of biliary lithiasis is therefore not yet clearly defined. It seems plausible that if gallbladder function is intact then the organ should be preserved, adopting either PCCL or ESWL as treatment depending on the stone burden. When the gallbladder no longer functions, surgical excision through either open or laparoscopic means should be the treatment of choice (Fig. 3).

Salivary gland stones

The safe, well tolerated treatment record of ESWL for urinary tract and biliary stones has initiated attempts to treat salivary gland stones (Iro *et al.*, 1989). Initial trials have shown promise for stones ranging from 2 to 15 mm, in either the parotid or

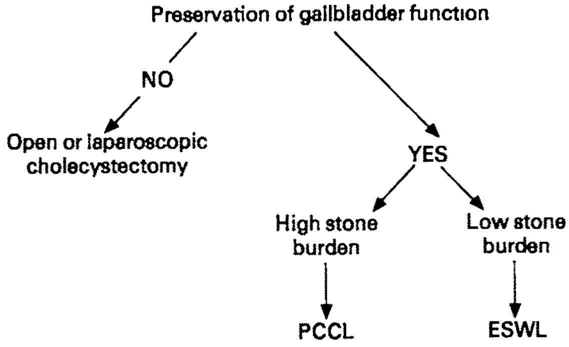
Preservation of gallbladder function
NO
Open or laparoscopic cholecystectomy
YES
High stone burden
Low stone burden
PCCL
ESWL

Fig. 3 Suggested management of symptomatic gallstones.

submandibular gland, that could not be removed intra-orally. The efficacy of this form of treatment requires further clinical trials.

Future Trends

Even if impaired renal function and hypertension prove to be long-term side effects of ESWL, the lithotripsy revolution is set to continue. In the management of a urinary tract stone, these risks and the patients' expectations for minimally invasive procedures are compared with those of open or percutaneous surgery. Open surgery produces greater renal trauma, even under regional hypothermia (Wickham and Mathur, 1971), with greater physiological disturbance and the need for blood transfusion, together with the hazards of wound infection, urinary fistulae and the enormous psychological stress of undergoing major surgery. For these reasons the indications for lithotripsy, in combination with minimally invasive surgery, have expanded and continuing technological advances mean that the end-point in development has not been reached. What improvements will the next generation of lithotripters have? It is anticipated that all machines will have both X-ray and ultrasound scanning to facilitate imaging of all stones. The efficiency of shock wave delivery to the stone could be improved by: (1) "image analysis" that would identify when the stone is within the focus of the shock wave, and only then allow wave generation, (2) a lock-on device that would cause the shock wave focus to move with the stone during respiration, and (3) the focus size and focal length could be adjusted, depending on the size and position of the stone being treated.

These technical advances would aim to produce stone destruction using the minimum number of shock waves and so reduce the long-term and short-term side effects to a minimum. This aim may also be furthered by novel methods of shock wave generation with altered wave characteristics that have less detrimental bioeffects on soft tissue. It is hoped that such research into shock wave technology might identify the parameters that could influence the severity of tissue injury and thus introduce "safe limits" within which ESWL can be conducted.

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Diagnostic and Surgical Aspects of Renal Carcinoma with Involvement of the Inferior Vena Cava

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Summary—Over the past 10 years, 13 patients presented with operable renal carcinoma and tumour extension within the inferior vena cava. This was diagnosed accurately in all but 1 patient, using ultrasound.

Radical nephrectomy with removal of tumour within the inferior vena cava was performed in all 13 cases, 2 requiring cardiac bypass. There were no operative deaths and 6 patients remain alive and well with a mean follow-up of 2 years. The presence and level of vena caval extension did not appear to have an adverse affect on prognosis.

Extension of tumour into the inferior vena cava occurs in about 5% of patients presenting with renal carcinoma (Marshall *et al.*, 1970). Historically such patients were regarded as representing a very poor prognostic group, and indeed were frequently deemed inoperable (MacDonald and Priestley, 1943). However, in 1972 Skinner *et al.* quoted a 5-year survival rate of 55% for patients with inferior vena caval extension, and in 1987 Emmott *et al.* concluded that, with aggressive management, survival rates approaching those for contained renal carcinoma could be achieved. We have therefore reviewed our own experience over the last 10 years.

Patients and Methods

Thirteen patients with renal carcinoma had involvement of the inferior vena cava at presentation: 11 men and 2 women, with a mean age of 53 years (range 32–72). Signs of inferior vena caval obstruction had developed in 4 patients: there were 2 varicoceles and 2 cases of bilateral deep vein thrombosis.

Diagnosis

Apart from the first patient, who presented before high quality real-time ultrasound was available, all patients were investigated using combinations of ultrasound (Fig. 1), CT scanning and venography to diagnose caval involvement. In those patients in whom tumour thrombus extended above the diaphragm, echocardiography was performed to exclude atrial involvement. Metastatic disease was

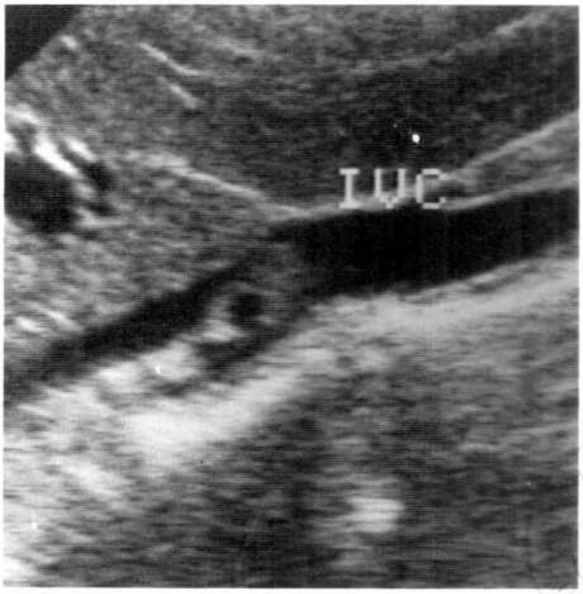

Fig. 1 Ultrasound showing tongue of tumour within inferior vena cava.

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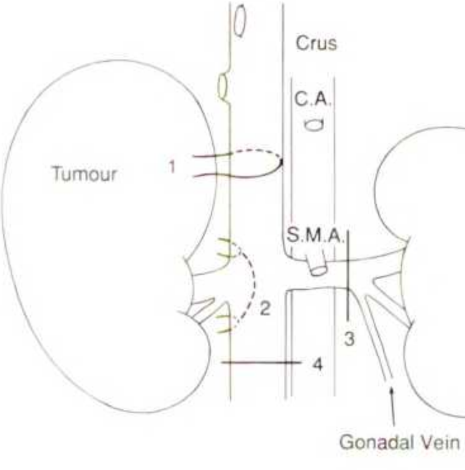
excluded as far as possible by routine methods including liver function tests, liver ultrasound, chest X-ray and bone scan. One patient in the series was known to have a solitary pulmonary metastasis at diagnosis.

Surgery

Thoraco-abdominal incision gave excellent vascular access for right-sided tumours and was used for 5 of the 6 right-sided lesions. For the 7 left-sided tumours a long midline incision with sternal splitting when necessary was used for all but 1 case. Cardiac bypass was required in 2 cases.

Mobilisation of the tumour-bearing kidney and ligation of its renal artery was performed by the urologist as in radical nephrectomy. Vascular control of the inferior vena cava was achieved by the vascular or cardiothoracic surgeon by gently occluding the inferior vena cava below the tumour thrombus, and occluding the contralateral renal vein. A sling was placed around the infrahepatic vena cava above the renal veins (Fig. 2). An elliptical incision was made in the vena cava around the renal vein ostium between stay sutures, and the tumour thrombus was drawn out by gentle traction with the nephrectomy specimen *enbloc*. This was feasible because the tumour thrombus had a firm non-friable consistency and did not invade the caval wall. Back-bleeding was then controlled using the sling already placed above the renal veins, and the venacavotomy was closed using a prolene suture. The liver was not mobilised routinely and no attempt was made to control the hepatic veins.



1. Sling
2. Venacavotomy between stay sutures

3,4. Soft clamps

Fig. 2 Vascular control.

Of the 2 patients who underwent cardiac bypass, 1 had gross atrial extension which was "mushroom-shaped" and had to be delivered via the atrium separate from the nephrectomy specimen.

Results

Diagnosis. In all but 1 case ultrasound accurately demonstrated involvement of the inferior vena cava (Table 1), and this 1 false negative was reported as equivocal and CT scanning was recommended. Of the 4 patients with suprahepatic extension, echocardiography accurately diagnosed atrial extension in the 1 case where it was present (Fig. 3) and there were no false positives.

Surgery. In all cases complete removal of the tumour thrombus was achieved; this included 1 patient in whom a fragment became detached, necessitating prompt thoracotomy for its retrieval. Two patients with suprahepatic tumour extension underwent cardiac bypass. There were no perioperative deaths.

Survival. Of the 13 patients in this series, 6 remain alive and well (Table 2). Five of the 7 deaths occurred secondary to disseminated renal carcinoma. The patient known to have a solitary pulmonary metastasis prior to his initial surgery had a right middle lobe lobectomy and survived a further 3 years.

Discussion

Vena caval extension should be excluded in all patients with renal carcinoma, since less than half have clinical signs of vena caval obstruction. Ultrasound is an accurate diagnostic technique in these circumstances (Webb *et al*., 1987) and is the investigation of choice because it is painless, readily available and non-invasive. In this study of 13 patients it yielded only 1 false negative result and even this was recognised as equivocal. Magnetic resonance imaging is also very accurate (Horan *et al*., 1989) and is ideal for cases where ultrasound is unsatisfactory.

The variety of operative approaches for vena caval tumour extension makes accurate pre-operative assessment mandatory. For those cases in which tumour thrombus remains infrahepatic an abdominal approach with control of the contralateral renal vein and the infrarenal vena cava is adequate. However, when thrombus extends higher into the retrohepatic vena cava, surgical technique

Table 1 Diagnosis

Patient no.	*Age (years)*	*Sex*	*Clinical signs*	*Diagnostic investigation*
1	55	M	Nil	Ultrasound Confirmed by CT
2	44	M	Nil	Ultrasound
3	55	M	Bilateral DVT	Ultrasound Confirmed by CT
4	68	M	Nil	Ultrasound Confirmed by CT
5	51	M	Nil	Surgery (Ultrasound equivocal)
6	55	M	Nil	Ultrasound CT unhelpful
7	60	F	Nil	Ultrasound and CT: thrombus above diaphragm—?atrial Echo—normal
8	56	M	Varicocele	Ultrasound Confirmed by angiography CXR—single metastasis
9	32	M	Varicocele	Ultrasound
10	50	M	Nil	Inferior venacavography
11	72	F	Nil	Ultrasound Confirmed by CT
12	38	M	Bilateral DVT	Ultrasound Confirmed by CT
13	50	M	Nil	Ultrasound Confirmed by CT Echo—atrial extension

DVT = Deep vein thrombosis.
CXR = Chest X-ray.

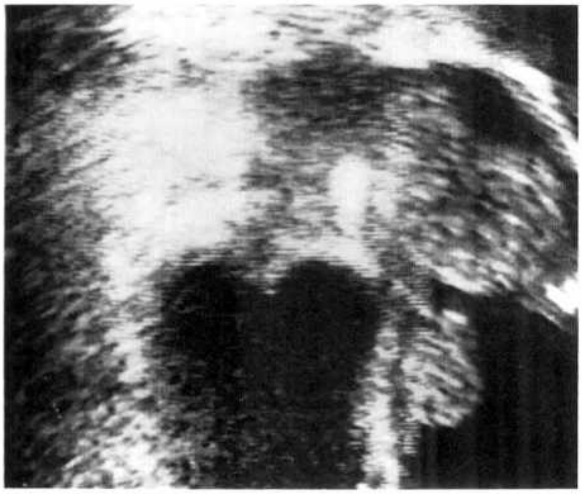


Fig. 3 Echocardiogram showing atrial extension.

becomes more controversial. Giuliani *et al.* (1989) recommended control of the intrapericardial portion of the inferior vena cava, mobilisation of the liver by division of the coronary and triangular ligaments, exposure of the hepatic veins and interruption of the hepatic circulation by clamping of the portal vein. Such complex surgery was not used in this series, and operative approach here was the same as for infrahepatic disease: this was not associated with any excessive morbidity.

In the event of supradiaphragmatic caval extension a number of techniques have been suggested, including the use of a Foley catheter through a small cavotomy, the balloon being inflated and used in a fashion similar to that of a Fogarty catheter in an embolectomy (Freed and Gliedman, 1975). However, this involves the risk of breaking off tumour emboli and there is no means of ensuring complete tumour removal. Skinner *et al.* (1972) advocated atrial occlusion with a Satinsky clamp to avoid cardiopulmonary bypass, but this is of value only when the tumour barely reaches the atrium, and it represents unnecessary risk when cardiopulmonary bypass is readily available. The latter affords excellent access, allowing safe complete tumour thrombectomy with a bloodless field. The only disadvantage is that heparinisation requires very thorough haemostasis, and 1 of the 2 patients undergoing cardiac bypass required re-exploration for bleeding within the immediate postoperative period.

Complete removal of tumour thrombus was

Table 2 Distribution of Tumour Extension and Survival

Patient no.	*Pathological spread* Venous extension	Fat	Nodes	Prognosis
1	Suprahepatic	+	−	Alive 5 years
2	Suprahepatic	+	−	Alive 2 years
3	Infrahepatic	+	−	Alive 2 years
4	Infrahepatic	−	−	Alive 6 months
5	Renal	−	−	Alive 6 months
6	Suprahepatic	−	−	Alive 4 months
7	Infrahepatic	+	+	Died 4 years—metastatic disease
8	Infrahepatic	+	−	Died 3 years—metastatic disease
9	Infrahepatic	+	+	Died 1 year—metastatic disease
10	Suprahepatic	+	−	Died 1 year—metastatic disease
11	Infrahepatic	−	−	Died 9 months—perforated diverticular disease
12	Infrahepatic	+	−	Died 6 months—metastatic disease
13	Right atrium	+	−	Died post-op.—gastrointestinal haemorrhage

achieved in all patients and is essential if the procedure is to be curative: in a large series from the Mayo clinic, incomplete removal was associated with a 5-year survival rate of 17.5% as compared with 68% when this was complete (Neves and Zincke, 1987).

The overall survival rate of 42% (mean follow-up 2 years currently) is consistent with that of other series. Although the numbers are small, there was no correlation between level of vena caval extension and prognosis, as previously suggested by Sosa *et al.* (1984). Only 1 patient was known to have metastatic disease at the time of surgery, and following right middle lobectomy for this solitary pulmonary deposit he survived a further 3 years. Surgery is indicated in such patients (Tolia and Whitmore, 1975).

In conclusion, with a current survival rate of 42% and in the absence of any operative deaths, surgery is indicated in patients with renal carcinoma involving the inferior vena cava. Ultrasound accurately demonstrates involvement of the inferior vena cava in the majority of such cases, and CT and MRI scans should be reserved for cases where doubt remains.

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Renal Carcinoma with Inferior Vena Cava Malignant Thrombosis

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Summary—During an 11-year period a total of 314 patients underwent surgery for renal carcinoma; 70 had venous extension of the tumour, 31 had extension to the main renal vein and were staged V1 and 39 had involvement of the inferior vena cava and were staged V2.

Special attention was paid to the latter group, which was divided into 2 subgroups: V2a for caval extension without ingrowth and V2b for caval extension with infiltration of the caval wall. Thirty-eight patients with caval involvement underwent surgery, with a 13% post-operative mortality rate.

Most of the patients with malignant caval ingrowth (V2b) had concomitant lymph node and distant metastases. However, some had negative lymph nodes and no metastases at the time of operation.

Perifascial nephrectomy associated with caval tumour removal or lateral subhepatic caval resection for patients staged V2aN0M0 significantly increased the survival rate when compared with that of patients with no surgery on the obstructed vena cava.

Total resection of the completely obstructed subhepatic vena cava for patients staged V2bN0M0 has limited indications but, in selected cases, may prolong survival.

This retrospective study supports the reintroduction of indicator V in the TNM staging of renal carcinoma and suggests the splitting of stage V2 into V2a for patients with free-floating caval extension and V2b for caval thrombus with ingrowth and caval wall infiltration.

Involvement of the inferior vena cava in patients with renal carcinoma is not uncommon (4–10%) (Marshall and Reitz, 1985), but its significance remains controversial. This complication has always been associated with a poor outcome, with the survival rate at 5 years being 25% after nephrectomy (Gilloz *et al.*, 1986). However, in recent years encouraging reports have been published following radical nephrectomy, caval thrombectomy or caval resection (Skinner *et al.*, 1972; Kearney *et al.*, 1981).

In some cases caval thrombi were extracted from the right atrium using either cardiopulmonary by-pass under cardioplegia and deep hypothermia (Belis *et al.*, 1989) or a venous by-pass (Atwood *et al.*, 1988).

Skinner *et al.* (1972) felt that survival was related more to perinephric invasion, lymph node and distant metastases than venous involvement, while Cukier and Charbit (1986) considered venous involvement to have a better prognosis than lymph node involvement.

Our findings do not contradict these statements, but we feel that venous involvement is underestimated and deserves more consideration as a predictive factor for survival. Several of the above controversies derive from inaccurate staging of venous extension of renal carcinoma.

Some clinical classifications disregard the fact that main renal vein involvement has a much better prognosis (30–60% 5-year survival rate) (Gilloz *et al.*, 1986) than caval tumour extension and in the same stage III they include renal vein, caval and nodal invasion (Merrin, 1979).

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The 1987 TNM classification of genitourinary tumours has omitted indicator V for vascular invasion, which is included as T3b for both renal vein and vena cava (Schröder *et al.*, 1988).

Other classifications are more accurate in staging venous involvement, as main renal vein thrombosis is labelled V1 (stage II) and caval thrombosis is labelled V2 (stage III) (UICC, 1974).

On the other hand, clinical data (including our findings) have shown that in many cases caval involvement represents a mere extension of the main renal vein thrombus within the caval lumen without ingrowth, while in other cases—fewer than in the first category—there is malignant invasion of the caval wall.

The significance of these 2 types of caval involvement seems to us to be of practical importance, since a free-floating caval thrombus can be completely extracted using appropriate surgical manoeuvres, with a reasonably good prognosis (Freed, 1980), while invasive caval thrombus, which is commonly accompanied by regional lymph node involvement, requires partial or even total subhepatic caval resection, operations which are both complicated and difficult (Komatsu *et al.*, 1985).

The purpose of this retrospective study was to support the reintroduction of V1 and V2 categories in the TNM staging system of renal carcinoma with venous extension and eventually to suggest the splitting of V2 into V2a for a non-adherent free-floating caval extension and V2b for an invasive intracaval extension.

Patients and Methods

Over the last 11 years (1977–1988) 314 patients underwent surgery for renal carcinoma. There were 196 males (62.4%) and 118 females (37.6%). Their mean age was 56 years (range 21–83).

The tumour was located on the right side in 160 patients (51%) and on the left side in 154 patients (49%).

According to the UICC (1987) TNM classification, 8 patients (2.5%) were staged pT1, 57 patients pT2 (18.2%), 184 patients pT3 (58.6%) and 65 patients pT4 (20.7%).

The regional lymph nodes were found to have been invaded in 84 patients (26.8%) and visceral metastases were present at the time of diagnosis in 51 patients (16.2%).

All patients were operated on by the same surgeon. Preference was given to the anterior transperitoneal approach (277 patients), while lumbar access was used in 35 patients, either because the diagnosis of cancer was uncertain or the patient was in poor condition. In 2 patients thoracophrenolaparotomy was performed.

The tumour-bearing kidney was excised in 91% of cases, 18 laparotomies remained "white" (5.7%); in 4 cases (1.2%) partial nephrectomy was performed and surgery was contraindicated in 5 cases (1.7%).

The overall post-operative mortality rate was 6.68% (21 patients). Fifteen of these fatalities occurred in patients with locally advanced disease, when surgery was overestimated and extensive resection of adjacent involved organs was performed: pancreatocolectomy (2), partial hepatectomy, cholecystectomy and right hemicolectomy (4), lateral excision of duodenum with ileal patch (3) and left hemicolectomy (6).

Special attention was paid to venous involvement. Of 314 patients, the tumour extension reached but remained confined to the main renal vein in 31 cases (9.8%), while in 39 patients (12.4%) the tumour extended to the inferior vena cava. In this latter group the tumour was right-sided in 27 patients, left-sided in 11 and in 1 instance the inferior vena cava was directly invaded by an upper pole right renal carcinoma.

According to the classification of Kearney *et al.* (1981), 33 patients had the upper limit of caval thrombus below or not above the posterior edge of the liver; in 5 cases the thrombus was retrohepatic and 1 patient had right atrial extension.

The diagnosis of caval thrombosis was suspected in patients with a non-functioning kidney, recent varicocele, swelling of the lower limbs and cavo-

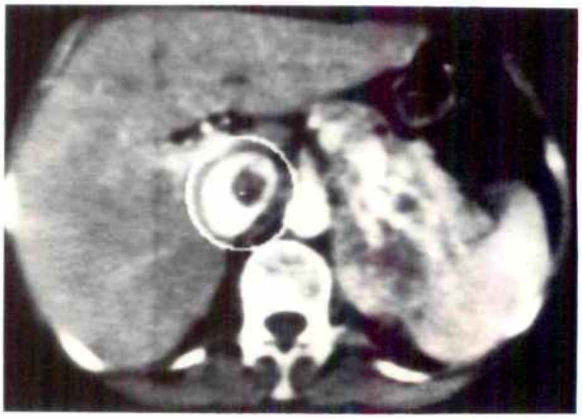

Fig. Patient with left renal carcinoma and extension within the intrahepatic vena cava. Free-floating intracaval thrombus stage T3N0M0V2a.

caval type subcutaneous venous collateral circulation. However, in most cases clinical symptoms were absent. In our experience the urographically silent kidney is highly suggestive of either total parenchymal tumour destruction or caval thrombus.

Although heavy proteinuria is considered indicative of caval obstruction, only 1 patient was admitted with the pseudonephrotic syndrome (generalised oedema and ascites) and this subsided after nephrectomy.

In most patients, the diagnosis of caval thrombosis was established with reasonably good accuracy either on computed tomography (CT) (80.4%) or echography (89%).

Venacavography was reserved for patients suspected on CT or echography of having caval obstruction.

The diagnosis of caval thrombosis was confirmed by surgery in 38 patients; 1 patient did not undergo surgery.

As mentioned above, according to surgical exploration and pathological examination of the specimen, caval thrombosis was labelled V2a when the thrombus extended from the main renal vein within the caval lumen, whose endothelial lining remained untouched, and V2b in cases of tumour extension with intracaval ingrowth, *i.e.* with caval wall penetration. Accordingly, 18 patients were staged V2a and 20 patients V2b.

Results

In the group of patients with non-adherent intracaval thrombus (V2a), all tumours were located on the right side: in most cases there was no local lymph node invasion and no metastases (Table 1).

In 17 patients perifascial nephrectomy and limited pericaval lymphadenectomy associated with thrombus extraction were performed, either by cavotomy or lateral resection of vena cava (Table 1).

There were 2 post-operative deaths, due to myocardial infarction on the seventh day and to pulmonary embolism on the eleventh day.

In 1 patient with caval extension of tumour staged pT3N3V2aM0G3, the vena cava could not be dissected because of lymph node enlargement and only simple nephrectomy was performed. The patient died 10 months post-operatively. The remaining 15 patients were followed up for at least 1 year after surgery (Table 1).

Twenty patients staged V2b had malignant caval thrombosis invading either a limited area of the caval wall (15 patients) or involving most, if not the full length of the abdominal vena cava (5 patients). All but 2 patients had enlarged pericaval lymph nodes and in 5 cases metastases were present. All patients were surgically explored.

In 5 patients the abdominal vena cava was resected from its origin to the posterior liver edge

Table 1 Survival of Patients with Renal Carcinoma and Inferior Vena Cava Thrombosis Staged V2a. Nephrectomy and Inferior Vena Cava Thrombectomy or Lateral Caval Resection

Patients	*Stage*	*Post-operative survival in months*	*Status*
1	pT3pN0M0V2aG2	146	Alive, free of cancer
2	pT2pN0M0V2aG2	48	Alive, free of cancer
3	pT2pN0M0V2aG2	72	Natural death
4	pT3pN2M1Hep.V2aG3	24	Died of cancer
5	pT3pN2M1Hep V2aG3	6	Died of cancer
6	pT2pN0M0V2aG2	36	Alive, free of cancer
7	pT3pN0M0V2aG3	48	Alive, free of cancer
8	pT3 pN3M1Oss.V2aG3	24	Alive, with vertebral metastases
9	pT3pN0M0V2aG2	18	Alive, free of cancer
10	pT3pN0M0V2aG3	12	Alive, free of cancer
11	pT3pN0M0V2aG2	24	Alive, free of cancer
12	pT4pN0M0V2aG2	12	Alive, free of cancer
13	pT3pN0M0V2aG2	20	Alive, free of cancer
14	pT3pN0M0V2aG3	12	Alive, free of cancer
15	pT3pN0M0V2aG2	12	Alive, free of cancer
16	pT3pN0M0V2aG2	—	Post-operative death—myocardial infarction
17	pT3pN0M0V2aG3	—	Post-operative death—pulmonary embolism
18	pT3pN3M0V2aG3	10 (no surgery on vena cava)	Died of cancer

and removed *en bloc* with the right kidney and lymph nodes. The left main renal vein was resected with preservation of the left spermatic vein and adrenal veins.

Two patients had an uneventful post-operative course, 3 developed acute renal failure and were treated by haemodialysis (2 recovered fully and 1 died of uraemia) (Table 2).

In 2 patients with right renal carcinoma staged N0V2b, perifascial nephrectomy was associated with lateral resection of the subhepatic vena cava and the adherent intracaval thrombus was removed. There was no post-operative renal failure or lower limb oedema (Table 3).

In 10 patients no attempt was made either to relieve the caval obstruction or excise the thrombotic vena cava. Simple nephrectomy was performed to alleviate pain and to control haematuria; 2 laparotomies remained "white" (all with suspected left kidney tumours) and 1 patient died during surgery (due to inadvertent thrombus fragmentation and pulmonary embolism) (Table 4).

The overall post-operative mortality rate for patients with malignant thrombosis of the vena cava was 13% (5/38).

To establish whether tumour extension to the vena cava provided independent prognostic information as to the presence or absence of lymph node metastasis all patients were divided into 4 groups:

(1)	N0/V2a	(14 patients)
(2)	N+/V2a	(4)
(3)	N0/V2b	(2)
(4)	N+/V2b	(15)

For each group the probability of survival was calculated according to Chin (1984) for the first 2 post-operative years and the following data were obtained:

(1) N0/V2a: $P3 = 0.88$
(2) N+/V2a: $P1 = 0.19$
(3) N0/V2b: $P4 = 1$
(4) N+/V2b: $P2 = 0.04$

The probability of survival was calculated for the first 2 years after surgery because the patients staged N+/V2a and N+/V2b were followed up for a maximum of 2 years.

The difference between the 4 probabilities was tested by pairs and was found to be significant ($P < 0.001$).

Discussion

Perinephric invasion, lymph node involvement and distant metastases are reliable predictors of post-

Table 2 Survival of Patients with Renal Carcinoma and Abdominal Vena Cava Invasion Staged V2b. Nephrectomy and Total Resection of Subhepatic Vena Cava

Patients	*Stage*	*Operation*	*Post-operative survival in months*	*Status*
1	pT4pN2M0V2bG3	Total abdominal caval resection and nephrectomy	20	Died of cancer
2	pT3pN3M1Hep.V2bG3	Total abdominal caval resection and nephrectomy	6	Died of cancer
3	pT3pN2M1Hep.V2bG3	Total abdominal caval resection and nephrectomy	—	Post-operative death—uraemia
4	pT4pN2M0V2bG2	Total abdominal caval resection and nephrectomy	16	Alive
5	pT3pN2M0V2bG2	Total abdominal caval resection and nephrectomy	18	Died of cancer

Table 3 Patients with Renal Carcinoma and Inferior Vena Cava Thrombosis Staged V2b. Right Nephrectomy and Lateral Resection of Subhepatic Vena Cava

Patients	*Staged*	*Operation*	*Post-operative survival in months*	*Status*
1	pT3pN0M0V2bG2	Lateral resection of abdominal vena cava and nephrectomy	48	Alive
2	pT3pN0M0V2bG2	Lateral resection of abdominal vena cava and nephrectomy	13	Alive

Table 4 Patients with Renal Carcinoma and Abdominal Vena Cava Thrombosis Staged V2b—No Attempt to Relieve Caval Obstruction. Palliative Simple Nephrectomy

Patients	*Stage*	*Operation*	*Post-operative survival in months*	*Status*
1	pT3pN2M0V2bG3	Nephrectomy	12	Died of cancer
2	pT4pN3M1Hep.Oss.V2bGx	Inoperable	4	Died of cancer
3	pT3pN2M1Hep.Oss V2bG3	Nephrectomy	3	Died of cancer
4	pT4a+bpN2M0V2bGx	Inoperable	2	Died of cancer
5	pT3pN3M0V2bG3	Nephrectomy	3	Right colon invasion and obstruction
6	pT3pN2M0V2bG1	Nephrectomy	Not known	—
7	pT4bpN2M0V2bG3	Nephrectomy	12	Died of cancer
8	pT3pN2M1Hep.V2bG3	Nephrectomy	—	Died of pulmonary embolism on 11th post-operative day
9	pT3pN2M0V2bG3	Nephrectomy	14	Vertebral metastases and paraplegia
10	pT3pN2M0V2bG3	Nephrectomy	—	Intraoperative death—pulmonary embolism

operative survival in patients with renal carcinoma. However, progression of a malignant thrombus within the abdominal vena cava could significantly alter both staging and prognosis and should be assessed before surgery.

Current imaging methods (CT, echography, vena cavography) delineate an intracaval thrombus accurately and prepare the surgeon for an adequate management protocol.

Horan *et al.* (1989) emphasised the accuracy of the combination of vena cavography and magnetic resonance imaging for identification of venous extension of renal carcinoma.

It is surprising that some clinical classifications of renal carcinoma pay little attention to venous involvement and make no prognostic distinction between a non-adherent intracaval thrombus and one with ingrowth. This difference is convincingly demonstrated by our data, since most patients with invasive caval thrombus had positive lymph nodes (15/17) and 5 also had distant metastases.

In 5 of these patients perifascial nephrectomy and total resection of the subhepatic vena cava was tried "as a desperate appliance to relieve a desperate grown disease" (Hamlet, act IV, scene 3), with little benefit. Nevertheless, survival in this group was significantly longer than in patients treated by palliative nephrectomy.

The patients with non-invasive intracaval thrombus had a better survival rate because most of them had negative lymph nodes, no metastases and the intracaval thrombus could be completely extracted in all cases.

Patients living for many years after nephrectomy and caval thrombectomy (12 years in 1 case) (Table 1) are a stimulus for the accurate staging of renal carcinoma, including venous involvement, on which to base surgery.

Our data support the view that caval extension of renal carcinoma could occur independently of either lymph node involvement or metastases and so should form a separate category in the TNM classification, *i.e.* V1 for thrombosis of the main renal vein and V2 for abdominal caval involvement.

Our experience suggests that splitting the V2 category into 2 subgroups, namely V2a for non-adherent intracaval thrombus and V2b for invasive caval thrombosis, would increase the accuracy of staging and promote better management. In the present study, patients staged N0M0V2a had a better survival rate than those staged N0M0V2b.

In conclusion, we feel that no patient with renal carcinoma and vena caval extension should be denied surgery, provided the lymph nodes are negative and metastases absent.

Statistical analysis of our data demonstrated that a patient staged N+/V2a ($P1 = 0.19$) has a probability of post-operative survival almost 5 times longer than a patient staged N+/V2b ($P2 = 0.04$) and this supports our proposal to split V2 into 2 subgroups, respectively V2a and V2b even for patients with lymph node invasion.

Our clinical analysis confirms the value of nodal metastasis as a prognostic indicator, since patients staged N0/V2a may live 4.5 times longer than patients staged N+/V2a and 22 times longer than patients staged N+/V2b.

The group of patients staged N0/V2b is too small (only 2 cases) to permit valid conclusions, but more such patients, followed up for longer time periods, would encourage a more aggressive approach in cases of renal carcinoma with caval ingrowth. Pre-operative documentation of the presence and extent of vena cava involvement (CT, echography, vena cavography) is mandatory in all patients before surgical exploration.

For patients staged V2a, the non-adherent thrombus could be extracted by appropriate surgical manoeuvres, including co-operation with a cardiovascular surgical team.

Total resection of subhepatic vena cava for V2b staged patients has limited indications and should be reserved for selected N0M0 patients with right renal carcinoma. Whenever possible, lateral resection of this vein should be preferred.

All of our patients with left renal carcinoma staged V2b were surgical failures because of concomitant positive lymph nodes and distant metastases.

To date, we have not recorded spontaneous regression of metastases after nephrectomy for renal carcinoma.

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Role of Magnetic Resonance Imaging in Blunt Renal Parenchymal Trauma

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Summary—The accuracy of magnetic resonance imaging (MRI) in the evaluation of blunt renal parenchymal trauma was compared with that of contrast-enhanced computed tomography (CT) and ultrasonography (US) in a prospective study of 12 patients. CT was superior to other methods in identifying and characterising the renal parenchymal lesion, and both CT and US exceeded low field MRI in recognising a perirenal fluid collection. The role of high field MRI in the evaluation of blunt renal trauma requires further study.

Most surgeons agree that appropriate treatment of blunt renal trauma is based on prompt and accurate evaluation of the type and extent of the renal injury. Computed tomography (CT) is the most informative radiological study in renal trauma and is the examination of choice in patients suspected of having serious renal injury or associated injuries amenable to CT evaluation (Pollack and Wein, 1989).

Magnetic resonance imaging (MRI), however, is potentially attractive and has some advantages over CT: lack of ionising radiation, no routine need for intravenous contrast medium, ability to obtain axial, sagittal and coronal sections without reformatting, and absence of beam-hardening artifacts and artifacts from air contrast fluid level in the gastrointestinal tract (Hricak *et al.*, 1983).

Magnetic resonance imaging at 1.5 T has shown promising results in comparison with CT and US in the diagnosis of acute cervical spine trauma (Mirvis *et al.*, 1988a), traumatic diaphragmatic rupture (Mirvis *et al.*, 1988b), traumatic adrenal haemorrhage (Murphy *et al.*, 1988) as well as focal neoplastic lesions of the spleen (Hess *et al.*, 1988) and performed equally with CT in pre-operative staging of rectal cancer (Guinet *et al.*, 1990). In a case of traumatic disruption of the gallbladder, MRI at 0.5 T and CT both correctly identified the liver haematoma but MRI was better in recognising the fluid collection as non-bloody (Baumgartner *et al.*, 1988). In patients with chronic subdural haematoma, MRI at 0.17 T has been able to visualise the haematomas even in the isodense CT phase (Sipponen *et al.*, 1984).

This prospective study examines the value of MRI in the evaluation of blunt renal parenchymal injuries, especially compared with CT and US.

Patients and Methods

Starting on 1 May 1986, patients treated for blunt renal trauma in this hospital were routinely evaluated with US and/or contrast-enhanced CT and in selected cases with renal angiography (RA). Capacity allowing, MRI study of the kidneys was performed with as short a delay as possible. Patients with penetrating renal injuries, renal pedicle injuries and those undergoing surgical treatment for renal or associated intra-abdominal injuries before US/CT and MRI evaluations were excluded.

Low field MR images were obtained in a 0.02 T magnetic field (833 kHz, Acutscan, Instrumentarium Corporation) in transaxial and coronal planes using partial saturation sequences (PS) with a repetition time (TR) of 500 ms and an echo time (TE) of 40 ms for T1 images, and TR of 1000 ms and TE of 60 ms for T2 images. The acquisition of

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PS images was repeated 4 or 8 times for signal averaging, the section thickness was 10 mm, the matrix size was 256 × 256 and a U-coil was used.

High field MR images were obtained with a high field superconductive magnetic imaging unit with a magnetic field of 1.0 T (Magnetom 42 SP, Siemens AG) in transaxial, coronal and sagittal planes with TR of 500 ms, TE of 15 ms, 4 acquisitions and a matrix of 192 × 256 for T1 images, and TR of 2000 ms, TE of 90 ms, 2 acquisitions and a matrix of 160 × 256 for T2 images. A body coil was used and contrast enhancement of T1 images was obtained with intravenous Gadolinium-DPTA (Schering AG).

The CT examinations were performed with a Somatom DR 2 scanner (Siemens AG) with a section thickness of 8 mm using intravenous iohexol (Nyegaard) with a dose of 450 mg I/kg bodyweight for contrast enhancement. The US studies were performed with an RT 3000 (General Electric) real-time scanner with a 3.5 MHz linear array and 3.5 MHz electronic sector transducer. Routine method for renal angiography with selective catheterisation of the renal artery was used.

By 30 April 1990, 4 years since initiating the study, 12 patients fulfilling the criteria had been included. Their mean age was 35 years (range 15–76) and 11 were male. The trauma mechanism was sports injury in 5 cases, motor vehicle accident in 3, fall in 3 and assault in 1 case. The mean delay from injury to admission was 7.5 h (range 2.3–23.0). Five patients had a total of 7 associated injuries (chest wall 4, head, vertebral column and liver 1 each).

All 12 patients underwent US study with a mean delay of 1.8 days (range 0–8) from the injury. Contrast-enhanced CT was performed on 10 patients with a mean delay of 1.6 days (range 0–8). The mean delay for MRI in 12 patients was 10.3 days (range 1–37); in 6 cases the delay was less than 5 days. If the interval between MRI and US/CT was more than 7 days, US or CT was repeated if possible. In 11 cases the interval between MRI and US or CT was less than 5 days; in 1 patient with renal contusion the interval was 17 days.

In assessing the renal injury, 2 factors were studied: presence or absence of renal parenchymal lesion and perirenal fluid collection. The renal lesions were classified in 3 categories of severity modified after Sargent and Marquardt (1950): contusion (no parenchymal defect, no perirenal fluid collection), laceration (parenchymal defect ± perirenal fluid collection) and rupture/fragmentation (visible fragment).

None of the patients was treated surgically. There was no mortality and 5 patients had a total of 7 minor complications. The mean hospital stay was 11 days (range 1–21).

Results

In 4 cases classified as renal contusions, no parenchymal lesions or perirenal fluid collections were found in any of the radiological investigations performed. In 1 case (no. 11) CT showed an obvious haematoma in the renal pelvis.

A perirenal fluid collection was seen in 8 cases in at least 1 of the radiological investigations. In 7 of these a renal parenchymal lesion was visible (Table).

Contrast-enhanced CT identified all 8 perirenal fluid collections; US showed 7 of them and was suggestive in the remaining case (no. 3). MRI at 0.02 T demonstrated 4 perirenal fluid collections and was only suggestive in 3 cases—nos. 3, 7 and 8 (Fig. 1).

Four of the 7 patients with a renal parenchymal lesion were classified as rupture due to a visible fragment, which on 2 occasions was confirmed by renal angiography—no. 8 (Fig. 1) and no. 5 (Fig. 2). CT identified all 7 patients with parenchymal lesions. US showed the lesion in all 4 patients with renal rupture but missed it in 3 cases with laceration. MRI at 0.02 T showed the lesion in 2 cases—nos. 3 and 5—and missed the parenchymal lesion in 3 ruptures—nos. 7, 8 and 12 (Fig. 1)—and 1 laceration (no. 4). MR at 1.0 T did not show the laceration in case no. 10 (Fig. 3).

Table Value of Radiological Method in Finding Renal Parenchymal Lesion/Perirenal Fluid Collection in 12 cases of Blunt Renal Trauma

Case no.	*MRI*	*CT*	*US*	*Others*	*Final grading*
1	−/−	nd	−/−		Contusion
2	−/−	nd	−/−		Contusion
3	+/±	+/+	−/±		Laceration
4	−/+	+/+	−/+		Laceration
5	+/+	+/+	+/+	RA: +/−	Rupture
6	−/+	−/+	−/+		Laceration
7	−/±	+/+	+/+		Rupture
8	−/±	+/+	+/+	RA: +/−	Rupture
9*	−/−	−/−	−/−		Contusion
10*	−/+	+/+	−/+		Laceration
11*	−/−	−/−	−/−		Contusion
12	−/+	+/+	+/+		Rupture

* High field MRI. + Significant. ± Suggestive. − Insignificant. nd = Not done. RA = Renal angiography.

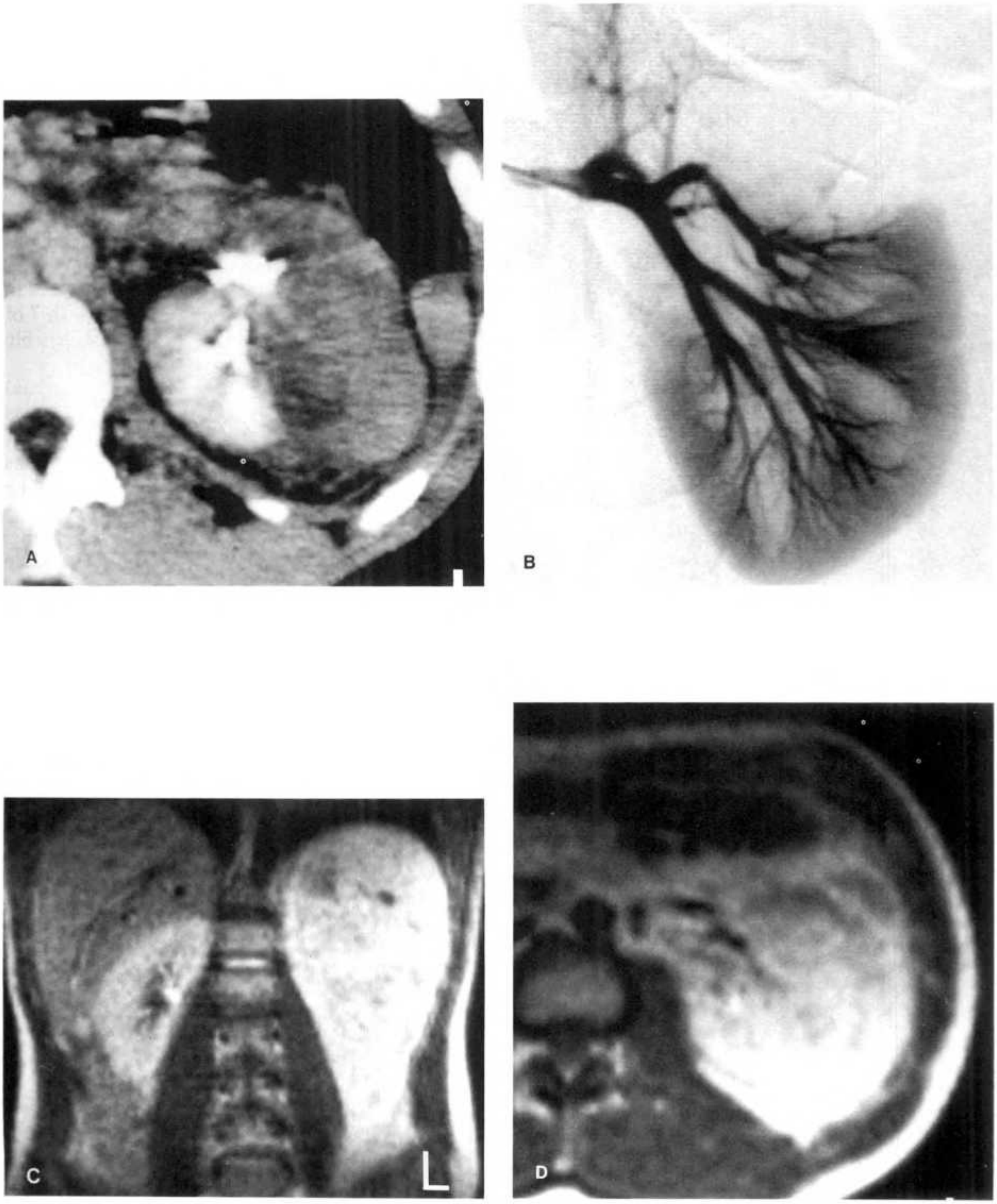

Fig. 1 Case no. 8: rupture of left kidney (L = left). (A) Contrast-enhanced CT showing rupture of left kidney with perirenal haematoma. (B) Arterial phase of selective left renal digital subtraction angiography showing smaller upper and larger lower fragment of ruptured left kidney. (C) and (D) MRI at 0.02 T, coronal (C) and transaxial (D) planes, T1 images showing heterogeneous outline of left kidney without signs of renal parenchymal lesion. The line between kidney and perirenal fluid collection cannot be identified.

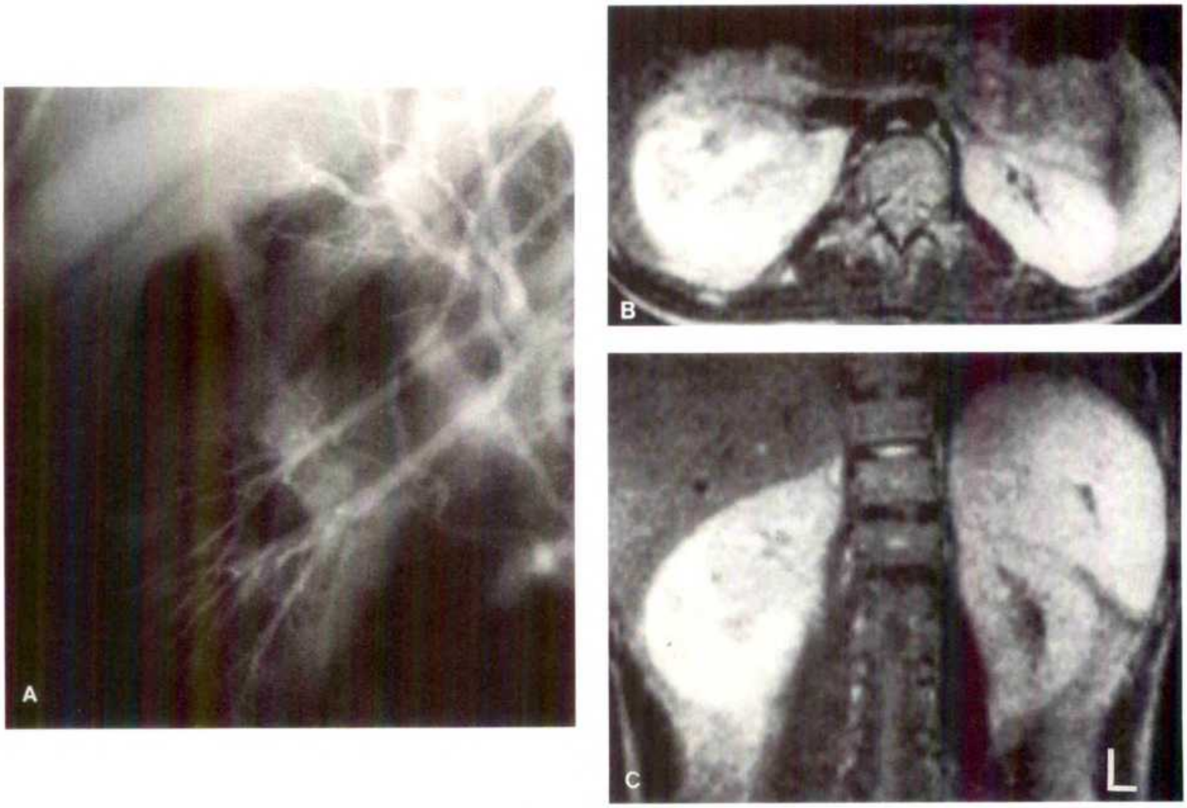

Fig. 2 Case no. 5: rupture of right kidney (L = left). (A) Renal angiogram showing 2 renal fragments. (B) and (C) MRI at 0.02 T, transaxial (B) and coronal (C) planes, T2 images showing a perirenal haematoma on right side; renal fragments can barely be identified.

Discussion

In assessing blunt renal trauma, an ideal radiological method should be capable of identifying correctly both the indirect and direct signs of a severe renal parenchymal trauma, *i.e.* the perirenal fluid collection and the parenchymal lesion itself respectively. MRI at 0.35–0.5 T seems to be more accurate than CT in characterising non-acute (>48 h old) haematomas and most of the non-bloody fluid collections (Unger *et al.*, 1986; Wall *et al.*, 1986; Baumgartner *et al.*, 1988), although Cohen *et al.* (1986) found accurate characterisation of haemorrhage and prediction of the age of clots impossible with MRI at 0.15 T.

MRI at 0.12–0.35 T has not shown any clear advantages over CT in assessing focal, non-traumatic renal lesions (Hricak *et al.*, 1983; Choyke *et al.*, 1984; Marotti *et al.*, 1987; Hricak *et al.*, 1988) and MRI at 0.02 T was inferior to CT in characterising renal masses (Lotz *et al.*, 1988).

Although promising results both in experimental and clinical studies on high field MRI assessment of kidney damage after extracorporeal shock wave lithotripsy (ESWL) have been reported (Baumgartner *et al.*, 1987; Neuerburg *et al.*, 1989), no previous studies on MRI in the evaluation of renal trauma have emerged.

The patients in this study were selected and quite homogeneous, since this is a referral hospital with a special urological unit. In a previous study from this hospital, 59% of patients with renal injury had laceration or more severe renal trauma and 41% of patients with blunt renal trauma had no associated injuries, resulting in under-representation of patients with renal contusions and severe multitrauma cases (Leppäniemi *et al.*, 1989). In addition, the design of the study presented here excluded patients with penetrating renal injuries and renal pedicle injuries. Although patients undergoing urgent surgical treatment were excluded, no patient was treated surgically after establishing the severity

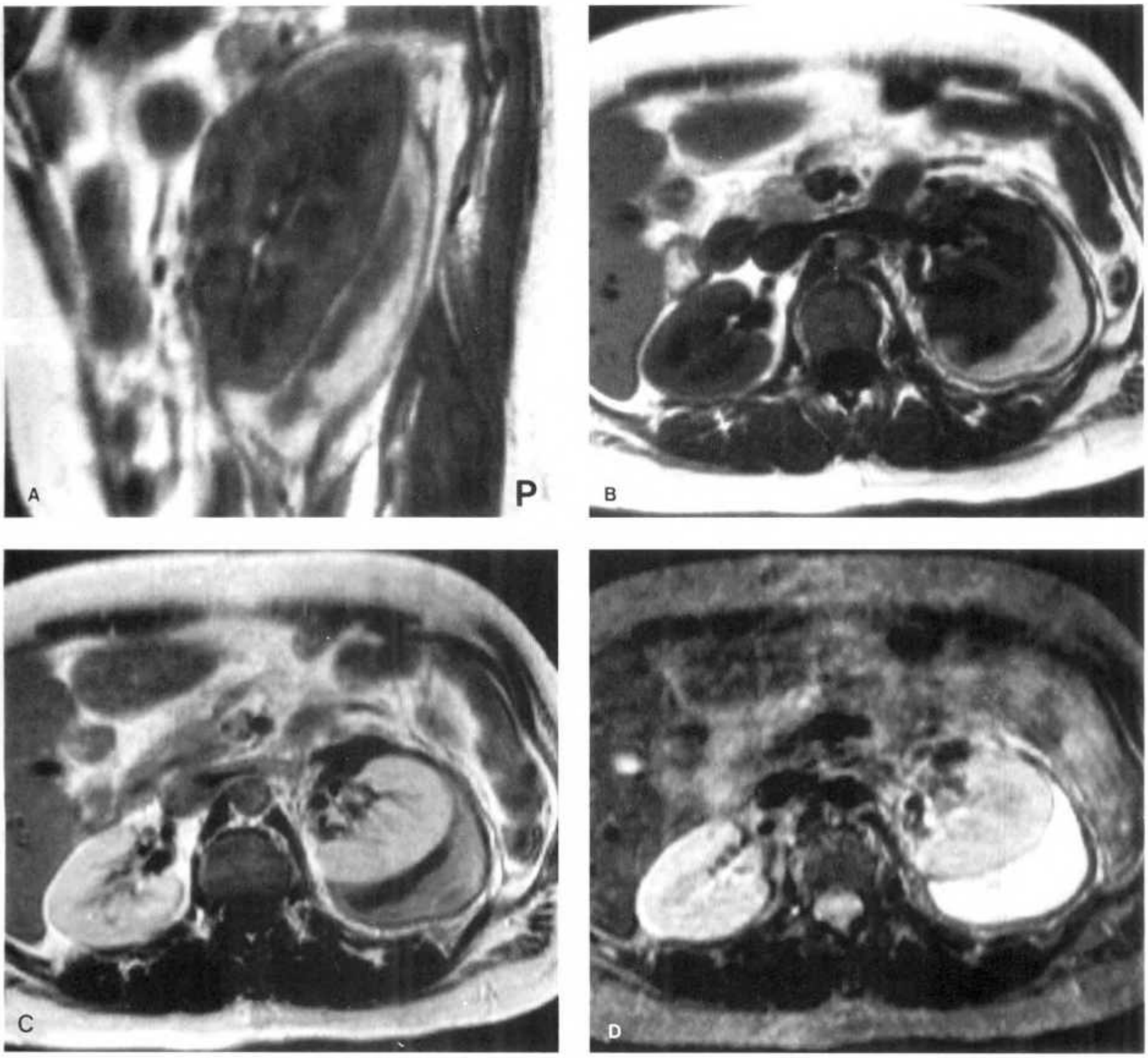

Fig. 3 Case no. 10: laceration of the left kidney, MRI at 1.0 T (L = left). Sagittal (A) and transaxial (B) T1 images show a heterogeneous left perirenal haematoma (P = posterior). (C) Contrast-enhanced T1 image demonstrates clearly the kidney contours without any signs of parenchymal lesion. (D) In a transaxial T2 image the perirenal haematoma gives a bright signal.

of the renal injury, even in 4 cases with renal rupture.

These results show that both contrast-enhanced CT and US are superior to MR at 0.02 T in identifying a perirenal fluid collection. MR at 1.0 T may be helpful in assessing the age of the perirenal haematoma and distinguishing the kidney from the haematoma, and it seems to exceed the accuracy of MRI at 0.02 T.

In recognising and characterising renal parenchymal lesions, CT was superior to all other methods used, with the possible exception of renal angiography. This series is too small for any conclusions to be drawn on MRI at 1.0 T but MRI at 0.02 T was clearly inferior both to CT and US in identifying the parenchymal lesion.

This study supports the results of McAninch and Federle (1982) that contrast-enhanced CT is the best method to define renal parenchymal injury. MRI at 0.02 T in its current stage of development is inferior both to CT and US. The experience with MRI at 1.0 T in renal trauma is still limited and warrants further studies.

It must be emphasised, however, that from a practical point of view, MRI imaging today does not offer anything new to the management of renal trauma. It is a time-consuming investigation and not very suitable for assessing acute renal injuries requiring urgent treatment. Another problem is the limited access to MRI imaging, since a majority of hospitals lack the equipment altogether.

Based on these results, we suggest the following protocol in assessing patients with blunt trauma to the trunk. Patients with macroscopic haematuria without obvious reason in the lower urinary tract should undergo US examination of the kidneys, even at the bedside. Patients with perirenal/retroperitoneal haematoma or suspected renal parenchymal lesion on US should have contrast-enhanced CT as soon as possible. Patients with non-enhancement of one or both kidneys on CT or on an abdominal radiogram taken after CT should undergo renal angiography to exclude renal pedicle injury. Patients allergic to contrast media could be evaluated with plain CT or high field MRI.

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Lumbar Nerve Root Compression and Interstitial Cystitis—Response to Decompressive Surgery

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Summary—An identifiable lumbar nerve root compression appears to cause urological dysfunction consistent with interstitial cystitis. Ten patients (9 females, 1 male) were evaluated for chronic pelvic pain. Cystoscopic and histological appearances were consistent with a diagnosis of interstitial cystitis. Magnetic resonance studies of the lower spine consistently demonstrated a lateral compression of the L5 dorsal nerve root. Decompression of the lateral foramina of L5 resulted in immediate relief of pain in 9 patients, who have been followed up for 6 months without a recurrence. Possible mechanisms involving sympathetic dystrophy of the pelvic plexus are reviewed.

Clinicians in various specialties have viewed with scepticism complaints by women of pelvic pain for which no obvious pathology can be found. The more "unusual" the symptoms, the greater has been the tendency to ascribe them to stress. However, for the vast majority of patients, physicians have failed to pursue further investigations in an attempt to establish an organic pathology. The painful bladder syndrome, interstitial cystitis, is perhaps one of the best examples of this situation. Until recently, specific histological diagnostic criteria were unavailable, leaving the urologist to surmise the diagnosis from the symptom complex, bladder capacity and endoscopic appearance. Once identified, treatment was directed towards symptomatic relief, since no causative agent could be elucidated which, through elimination, would resolve the pain.

The urological complaints of unremitting frequency, urgency and pelvic pain in the absence of infection have characterised a number of inflammatory syndromes, such as trigonitis, urethritis and chronic cystitis, all of which are now viewed as "stages" of interstitial cystitis. The gynaecological entities of broad ligament neuritis, chronic parametritis and pelvic congestion syndrome share many of the same complaints, including low back pain which radiates down the anterior and anteromedial aspects of the thigh and becomes worse with sitting and standing. However, as reported by Taylor (1954), back pain is rarely the primary complaint in these patients.

The peripheral nerve fibres to the bladder and urethra emanate from the spinal segments T10–L1 and S2–S4. These fibres are routed in nervi hypogastrici and nervi erigentes respectively. The autonomic contribution of the L5, S1 and S2 nerves leaves the vertebral foramina anteriorly to join the hypogastric nerve of the inferior mesenteric plexus. Together these fibres make up the pelvic plexus which then spreads along the lateral aspect of the rectum to innervate various pelvic organs. The highest density of adrenergic nerves is found in the trigone, bladder neck and proximal urethra, where they serve a sensory function and are involved with vascular innervation. Within each vertebral body and the adjacent cartilaginous end-plates are vascular channels with nerve fibres from the sympathetic trunk serving, in part, a nociceptor function. Because the cell bodies of visceral afferent fibres lie in the dorsal root ganglia, we investigated the association between lumbar nerve root compres-

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sion involving L5 as it relates to interstitial cystitis and its response to microsurgical decompression.

Patients and Methods

Nine female patients and 1 male patient presented with the urological complaints of severe frequency, urgency, nocturia and pelvic pain in the absence of infection. Gynaecological symptoms of clitoral hypersensitivity and dyspareunia were present in the women, while the man complained of perineal and meatal pain. In addition to their urological complaints, these 10 patients were questioned specifically about back discomfort and each vaguely admitted to pain radiating from the posterior buttocks to the lateral thigh which became worse with standing, sitting or exercise. These symptoms were suggestive of a compressive radiculopathy syndrome. However, all 10 patients related that their pelvic pain far outweighed any leg or back pain and denied they would have sought neurosurgical evaluation for these complaints. Urodynamic evaluation with synchronous cystometrography (CMG), electromyography (EMG) and uroflowmetry demonstrated pain upon distension of the bladder, detrusor myopathy with abdominal straining to void and pelvic floor dyssynergia.

The patients were evaluated with magnetic resonance scanning on a 1.5 T magnet and/or myelography followed by thin-section CT scan. Lumbar compression appeared to be consistently at the lateral gutter and exit foramina of the L5 nerve root, and foraminal compression was from a combination of facet hypertrophy of the mesial end tip of the sacral facet, as well as lateral rupture of the L5–S1 disc, resulting in a far lateral compression of the L5 dorsal nerve root (Fig.). This finding represents a distinctly different point of compression from the usual L5–S1 ruptured disc which compresses the transversing S1 nerve root.

Patients were cystoscoped under anaesthesia and found to have the diagnostic petechial haemorrhages seen with interstitial cystitis (Messing and Stamey, 1978). These glomerulations were present predominantly along the trigone and bladder neck and extended up the lateral walls of the bladder, excluding the dome. Histological examination confirmed the diagnosis of interstitial cystitis as defined by Gillespie *et al.* (1990) and Said *et al.* (1989). In each patient bladder capacity exceeded 700 ml, with a mean capacity of 837 ml indicating detrusor myopathy.

Urological management of these patients consisted of intravesical therapy (Gillespie *et al.*, 1985), dietary restriction of the arylalkylamines (Gillespie, 1986) and back and stomach strengthening exercises. Cholinergic stimulation with bethanechol chloride resulted in increased pressure and cramping, and was discontinued. While all patients noted some improvement in symptoms, there was no enduring change in either their pelvic or back pain. Selective nerve blocks were performed for diagnostic purposes either through a lumbar or pericervical/periprostatic approach with bupivacaine HCl 0.5% (Marcain) and betamethasone acetate suspension 6 mg/ml, resulting in complete temporary relief of their bladder pain. Patients were subsequently referred for surgery.

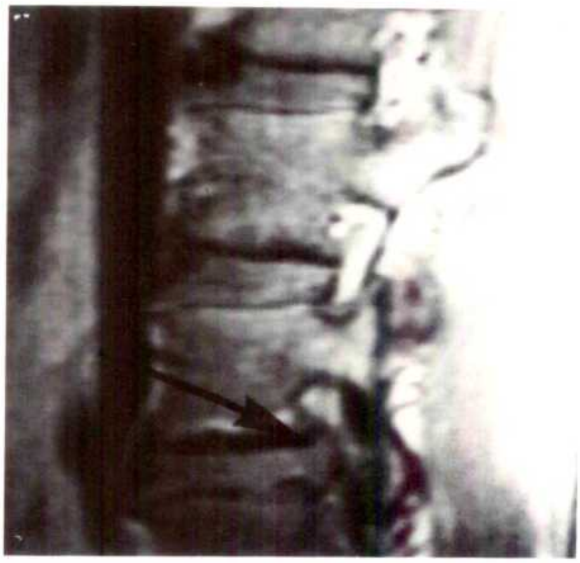

Fig. Intraforaminal disc herniation in the far lateral position at the congenital anomaly of an L5–L6 level. The L5 root is displaced upwards and compressed.

In order adequately to decompress the L5 foramina in 8 patients, a microsurgical approach was used. A medial facetectomy of the L5–S1 space was performed using a high-speed air drill, preserving the laminar arch and yellow ligament covering the dura. The lateral gutter was dissected, allowing access to the disc and L5 exit foramina in the far lateral position. This area is not well visualised through the traditional laminectomy approach. Adequate decompression was obtained by removal of the mesial edge of the tip of the S1 facet and, by angulating the operating microscope, visualisation of the superior lateral gutter allowed removal of any osteophyte spurring via the L5–S1 interspace. The remaining 2 patients did not require a facetectomy and underwent laser evaporation of their L5 discs on an out-patient basis.

Results

The initial response in 9 patients was so significant that they noted relief of their pelvic pain as soon as they regained consciousness in the recovery room, and progressive improvement was observed over the next 24 h, such that patients complained only of minimal back pain. Subsequent flares of urological complaints during the next few weeks seemed to parallel flares in leg and back pain with the usual post-operative swelling, and appeared to decrease by 6 to 8 weeks. Repeat urodynamic studies at 3 months no longer demonstrated pelvic floor dyssynergia, and the pain with distension was gone. The addition of bethanechol chloride at 12 weeks improved detrusor contractability without causing urgency in 3 patients with persistent detrusor myopathy, and dietary restrictions were discontinued in all patients without recurrence of pelvic pain. The patients have since remained stable and free of symptoms for 6 months. The remaining patient noted improvement in her back and bladder pain but still complained of frequency.

Discussion

The presence of chronic pelvic pain (CPP) in the female has often frustrated the clinician, resulting in unsatisfactory response to suppressive antibiotic therapy and even hysterectomy. These management failures are frequently labelled "psychosocial disorder" and recommended for therapy (Alsofrom, 1985). The debilitating symptoms of interstitial cystitis are such that many patients resort to urinary diversion or even cystectomy (Webster and Galloway, 1987).

The presenting urological symptoms of this subcategory of patients with interstitial cystitis overshadowed their neurological problems, and none of the patients associated the 2 problems. It is therefore essential that clinicians elicit a history of back and leg pain, even if it is dismissed as mild in nature when evaluating individuals with CPP. The symptom of clitoral pain or hypersensitivity is significant, as branches from the pelvic plexus innervate not only the ostium of the cervix and anterior vaginal wall, but also the clitoris and corpus cavernosum respectively. The pericervical ganglia are located in the connective tissue running along the uterovaginal junction, while the periprostatic ganglia are located within the neurovascular bundle which is enclosed by the lateral pelvic fascia. Pericervical/periprostatic nerve blocks should be used by diagnosticians in an effort to identify the involvement of a sensory, sympathetic disturbance in these patients.

The immediate response of this chronic syndrome to decompression raises questions of physiological mechanisms based on ischaemia or sympathetic discharge, much like reflex sympathetic dystrophy. It is well known that a fine plexus of nerve fibres similar to those seen in the urethra occurs in the lamina propria of the bladder wall (George and Dixon, 1986). Immunofluorescent staining of tissue from patients with interstitial cystitis, together with electron microscopy, demonstrates the loss of endothelial integrity with resultant leakage of fibrinogen into the interstitium and along the lamina propria (Gillespie *et al.*, 1990). This serves as a matrix for new vascular growth. Abnormal proliferation of small blood vessels has been identified as a hallmark of the endoscopic appearance of interstitial cystitis. Rapid generation of capillaries, defined as angiogenesis, can be triggered by intracellular hypoxia, acidosis, hypercarbia, hypokalaemia and hypoglycaemia, resulting in ischaemic vasodilatation and increased capillary membrane permeability (Knighton *et al.*, 1987). Even mild changes in blood flow cause large changes in shear, which are directly related to flow velocity and viscosity and inversely related to the internal diameter of the vessel. Pulsatile changes in the intrinsic blood supply, therefore, would result in reperfusion injury (Stein *et al.*, 1988). The appearance of petechial haemorrhaging after passive distension and decompression of the bladder in patients with interstitial cystitis is an example of such vascular perfusion alterations.

Delamarter *et al.* (1990), in their experimental model of lumbar spinal stenosis, demonstrated that as little as 25% constriction of the cauda equina resulted in venous congestion and leakage of dye in the root and dorsal root ganglion of the seventh lumbar nerve in dogs. It is apparent that the unmyelinated nerve terminals that comprise both the interstitial and perivascular receptor systems are bathed by the interstitial fluid within the tissues that contain them. A variety of polypeptide amines are capable of stimulating these nociceptor nerve endings and there is good evidence that these peptides, mainly substance P and vasoactive intestinal polypeptide (VIP), may be responsible for the transmission and modulation of our pain responses. The release of substance P from peripheral nerve endings has been shown to cause vasodilatation and plasma extravasation in the rat and guinea pig bladder (Saria *et al.*, 1983; Maggi *et al.*, 1987). Vaalasti *et al.* (1986) demonstrated that VIP-immunoreactive nerves were found subepithelially within the bladder and that they control subepithelial and vascular smooth muscle as it relates to blood flow. Efferent stimulation of the hypogastric nerves resulted in release of VIP to the local venous effluent, which in turn was accompanied by an increase in uterine venous blood flow. The venous pelvic congestion seen during laparoscopy in patients with CPP may be the result of increased release of these peptides.

An identifiable lumbar nerve root compression appears to cause urological dysfunction consistent with interstitial cystitis. It is additionally encouraging that functional return was not inversely predicated upon duration of lumbar nerve root compression, as one patient had a 5-year documented history of her ruptured disc in association with urinary symptomatology. This distinct subcategory of CPP patients does not represent the "classic" picture of interstitial cystitis, since bladder capacity was enlarged rather than decreased. Current literature has categorised these patients as having an "early" rather than "late" stage of this syndrome (Fall et al. 1987). Our experience with approximately 2500 patients does not support this hypothesis, since factors affecting vascular permeability were found to be more significant (Gillespie et al. 1990).

The identification of "asymptomatic" nerve root compression is not new to the urological literature. Emmett and Love (1971) reported 35 patients with negative neurological findings, equivocal myelograms and detrusor myopathy with urinary retention, who responded to discectomy at the L4 level. The absence of pain with distension was a hallmark of nerve root congestion at this level and this is consistent with our experience in patients seen for recurrent bacterial cystitis without pelvic pain.

The failure of 1 patient to improve urologically may be the result of a greater degree of stenosis, resulting in dystrophic damage to the extradural roots. Wallerian degeneration was seen in many sensory roots as a result of 50% constriction or more of the cauda equina, resulting in complete loss of cortical evoked potentials and neurological deficits. The use of somatosensory evoked potentials may predict the surgical outcome and is currently being investigated. The syndrome of urological dysfunction characterised by interstitial cystitis appears to be treatable by adequate decompression of the lateral L5 nerve root in this select subset of patients. Further long-term studies appear warranted and at present are under way.

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Bladder Dysfunction due to Human T-lymphotrophic Virus Type I Associated Myelopathy

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Summary—Bladder dysfunction is a major complication of human T-lymphotrophic virus type I associated myelopathy (HAM). Four patients (3 females and 1 male, aged between 23 and 44 years), who had suffered from HAM for an average of 6 years complained variously of difficulty in micturition, frequency, bed wetting and/or urge incontinence. They were investigated urodynamically. A significant amount of urine was retained in the bladder of 3 patients. During the storage phase, bladder sensation was well preserved in all 4 patients but severe uninhibited detrusor contractions were observed in 3. At micturition, detrusor contractility was present in 3 and completely lost in 1. Of the 4 patients with HAM, 3 suffered from detrusor hyper-reflexia and 1 from detrusor areflexia.

Since the new clinical entity, human T-lymphotrophic virus type I (HTLV-I) associated myelopathy (HAM), was described by Osame *et al.* (1986c), the relationship between chronic myelopathy and HTLV-I has generated much interest (Johnson and McArthur, 1987). HAM is endemic in southwestern Japan and is suspected to be the same as the disorder termed tropical spastic paraparesis (TSP), which is prevalent in the Caribbean (Gessain *et al.*, 1985). In addition to distubances of gait, bladder dysfunction is a clinical characteristic of HAM. Matsuo *et al.* (1989) reported that 20 of 21 patients with HAM had micturition problems. The objective of the present study was to evaluate the bladder dysfunction in 4 patients suffering from HAM.

Patients and Methods

The characteristics of the 4 patients are summarised in Table 1. They were followed up for 1 to 4 years (mean 2.4). They had initially visited the Department of Neurology for evaluation of spastic gait. The diagnosis of HAM was based on an increased titre of the antibody to HTLV-I in both the serum and cerebrospinal fluid. Symptoms of bladder dysfunction (bed wetting, frequency of micturition, urgency, urge incontinence, difficulty in micturition) developed at about the same time as the gait disturbance in all but 1 patient (case 4), whose difficulty in urination preceded the development of the spastic gait. All 4 patients urinated with the Valsalva/Credé manoeuvre when we first examined them. Urodynamic studies were performed before and after treatment with prednisolone and interferon-alpha by passing an 8 F double-lumen catheter into the urethra and placing a balloon catheter in the rectum while the patient was in a sitting position. A 30% contrast medium was infused into the bladder at a rate of 30 to 40 ml/min and the lower urinary tract was intermittently monitored by X-ray. The parameters observed were urinary flow rate, bladder pressure, and the abdominal pressure beside the urinary free flow rate. Electromyography was conducted in 1 patient via 2 surface electrodes. The methods, definitions and units used in this study conform with the standards recommended by the International Continence Society except where specifically noted.

Results

Free uroflowmetry revealed an intermittent flow pattern in 3 patients (Fig. 1) and a normal pattern

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Table 1 Details of Patients

	Patient no.			
	1	*2*	*3*	*4*
Sex	F	F	M	F
Age (years)	33	44	23	25
Duration of HAM (years)	8	10	5	1
Complaints	Difficulty in micturition and bed wetting	Urge incontinence and frequency	Urge incontinence and difficulty in micturition	Difficulty in micturition
Micturition	Valsalva/Credé	Valsalva/Credé	Valsalva/Credé	Valsalva/Credé
Transmission of infection	Mother-to-child	Mother-to-child	Mother-to-child	Blood transfusion

in 1 (case 4), in whom urination was assisted by abdominal straining. A significant amount of urine was retained in the bladder of 3 patients. Bladder sensation was well preserved in all 4 patients. Although severe uninhibited detrusor contractions were observed in 3, the detrusor contractions at micturition were weak and transient in 2 but well preserved in 1 (Table 2). Detrusor sphincter dyssynergia was confirmed in 1 patient both fluoroscopically and electromyographically (Fig. 2). These 4 patients had received treatment with prednisolone and/or interferon-alpha, which had little or no effect on the micturition disorders. Three of the 4 patients were subsequently placed on a regimen of clean intermittent catheterisation with no complication and the fourth required no treatment.

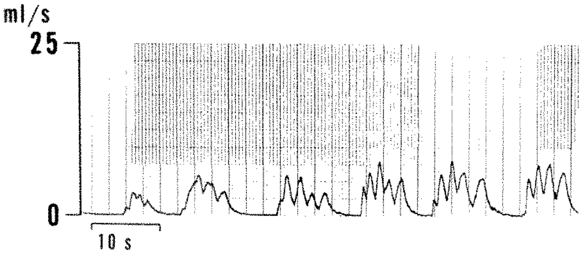

Fig. 1 Uroflowmetry in patient no. 1 shows intermittent voiding pattern.

Discussion

HTLV-I is a retrovirus that causes adult T-cell leukaemia (ATL). Recent findings indicate that the virus isolated from patients with HAM appears to be identical to that from patients with ATL (Yoshida *et al.*, 1987). HTLV-I is distinct from HTLV-III, which was isolated from patients with the acquired immune deficiency syndrome (AIDS), *i.e.* infected with the human immunodeficiency virus (HIV). Infection with HTLV-I is transmitted by 2 main routes: blood transfusions (Osame *et al.*, 1986b) and mother-to-child transmission (Osame *et al.*, 1986a). Three of our 4 patients were thought to have been infected via mother-to-child transmission at birth or during infancy. The fourth patient appeared to have contracted the virus via blood

Table 2 Urodynamic Data

	Patient no.			
	1	*2*	*3*	*4*
Uroflowmetry	Poor	Poor	Poor	Poor
Average residual urine (ml)	200	150	250	0
Cystometry				
FDV (ml)	150	150	170	80
MDV (ml)	220	200	300	200
UIC	Absent	Present	Present	Present
Det. cont.	Lost	Present	Weak	Weak
DSD	Absent	Present	Unknown	Unknown
Trabeculation	Slight	Slight	Slight	Absent
Reflux	Absent	Absent	Absent	Absent
Medical treatment	CIC	CIC	CIC	None

FDV: first desire to void. MDV: maximum desire to void. UIC: uninhibited contraction. Det. cont.: spontaneous detrusor contraction at voiding. DSD: detrusor sphincter dyssynergia. CIC: clean intermittent catheterisation.

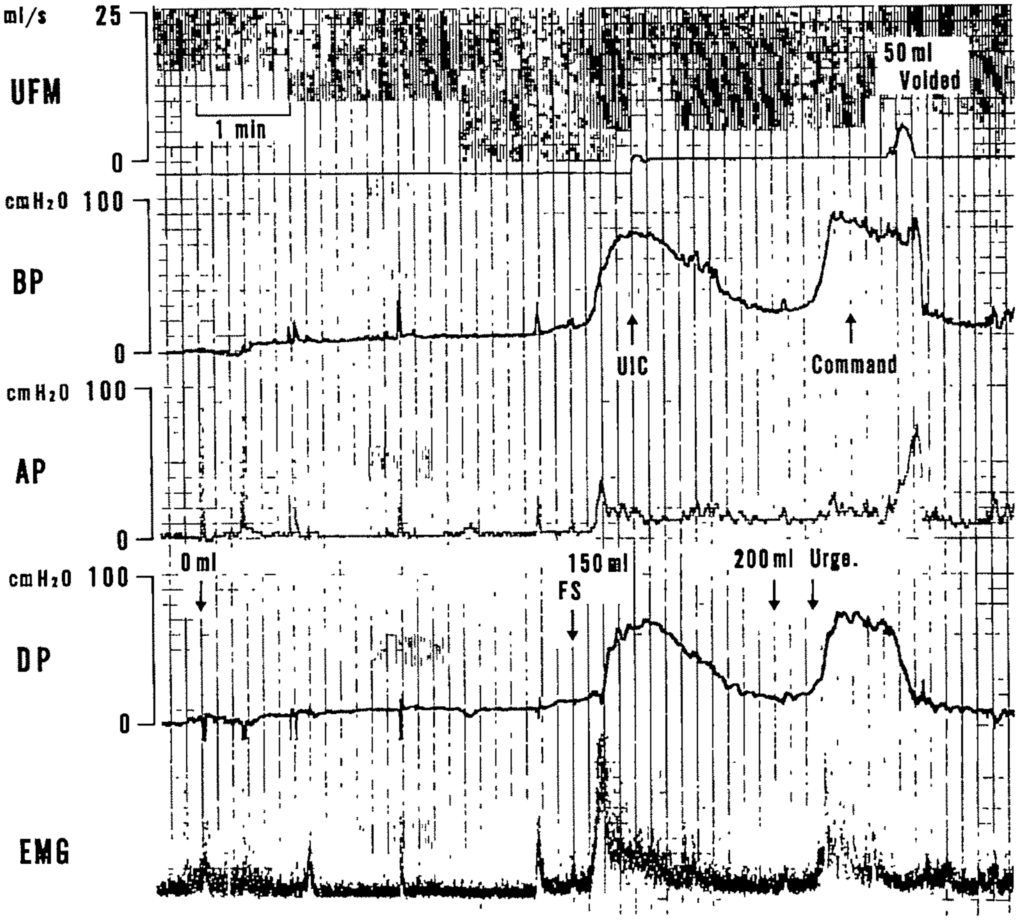

Fig. 2 Detrusor hyper-reflexia with detrusor sphincter dyssynergia observed in patient no 2. UFM: uroflowmetry. BP. bladder pressure. AP: abdominal pressure. DP: detrusor pressure, EMG: electromyography of external sphincter. UIC: uninhibited contraction. FS· first sensation. Command· command to void.

transfusion during cardiac surgery performed during childhood.

The clinical course of HAM is slow and progressive. Most patients develop urinary dysfunction and disturbances of gait. HAM is readily diagnosed by a positive finding for HTLV-I antibody in both the serum and spinal fluid (Osame *et al.*, 1987). Although approximately 90 to 100% of patients report micturition disorders (Matsuo *et al.*, 1989), few investigations have described the urodynamic findings. Subjective complaints include symptoms of both obstruction and urgency. The former implies a loss of effective detrusor contractility at micturition while the latter implies uninhibited contractions during the storage phase. The amount of residual urine was significant in 3 of the 4 patients. Although strong uninhibited detrusor contractions were observed in 3 patients, detrusor contractility at voiding was considerably impaired in 2 but normal in 1 who, however, was unable to void normally because of detrusor sphincter dyssynergia. Our findings are partially in accord with the report on HAM by Namima *et al.* (1990). These investigators examined 2 patients who retained a significant amount of urine in the bladder, 1 of whom demonstrated uninhibited contractions and detrusor sphincter dyssynergia, while the other had uninhibited contractions and a complete loss of detrusor contractility. The urodynamic findings varied from detrusor areflexia to detrusor hyperreflexia, probably depending on the extent of central nervous system involvement. The pathology of the bladder disorder is closely related to the diffuse lesion of the white matter which, at its onset, predominantly involves the thoracic cord (Arimura *et al.*, 1987). This would account for the hyper-reflexic bladder, with or without disco-ordination between the detrusor and the sphincter. At an advanced stage of the disease, the neurogenic lesion is thought to spread to other parts of the spinal cord, producing complete impairment of the sacral reflex arc.

Although it was suggested that the administration of prednisolone and/or interferon-alpha might improve the spastic gait of these patients (Matsuo *et al.*, 1989), these agents had little effect on the bladder disorder. At present, clean intermittent catheterisation, with or without anticholinergic medication, appears to be the treatment of choice for patients suffering from neurogenic bladder due to HAM.

In conclusion, urodynamic investigation of 4 patients with HAM revealed that 3 suffered from detrusor hyper-reflexia and 1 from detrusor areflexia. Clean intermittent catheterisation proved helpful in 3 while the fourth patient required no treatment.

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Reliability of the Urethral Closure Pressure Profile during Stress in the Diagnosis of Genuine Stress Incontinence

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Summary—Urethral pressure profile (UPP) measurements were recorded during stress using the method of Brown and Wickham in 981 patients with lower urinary tract symptoms. This procedure was used to identify patients with genuine stress incontinence (GSI). A clinical stress test in the supine and erect position served to confirm urinary leakage. GSI was diagnosed in 661 patients (67%), whereas no incontinence was demonstrable in 320 (33%). UPP during stress has a high sensitivity (93.3%) and specificity (82.5%). Compared with other urodynamic investigations, the ease with which it can be performed at the same time as other urodynamic procedures makes a reliable diagnostic adjunct in the assessment of patients with GSI.

Genuine stress incontinence involves the involuntary loss of urine from the bladder through the urethra following a sudden increase in intra-abdominal pressure without a detrusor contraction (Bates, 1976).

The field of urodynamics developed because physicians recognised that history, physical examination and other tests failed to distinguish between patients with GSI and those without. The early techniques of Brown and Wickham (1969) used a fluid perfusion system for measuring pressure within the urethra, while simultaneously monitoring bladder pressure. Static and dynamic urethral profilometry using microtip pressure transducers is now widely used (Asmussen and Ulmsten, 1975; Anderson *et al.*, 1983; Hilton and Stanton, 1983). However, urethral pressure profile measurements in the storage phase of the bladder are not regarded as the "gold standard" in the assessment of GSI, irrespective of the techniques used (Abrams *et al.*, 1988; Lose *et al.*, 1990). In addition to various measurements of the UPP at rest, the cough UPP was assumed to serve as a diagnostic test to verify GSI (Shepherd, 1985; Richardson, 1986).

Previous studies have involved only small numbers of women and so the aim of the present study was to evaluate the significance of the cough pressure profile (obtained by the method of Brown and Wickham (1969)) in a larger series. We were encouraged to use this test because it is simple, practical, and can be carried out at the same time as other urodynamic tests.

Patients and Methods

Complete urodynamic evaluations were performed in 981 women with lower urinary tract symptoms. Investigations included a detailed history, physical examination, urine analysis and culture, filling cystometry, and urethral pressure profilometry at rest and during stress in the sitting position. A clinical stress test in the supine and standing position, when the patients were asked to cough as forcefully as possible, was carried out to assess urinary loss objectively. Exclusion criteria were residual urine and isolated detrusor contractions during filling cystometry.

A 6-channel system (DISA 2100; Dantec Electronics, Skovlunde, Denmark) with open catheters (7F; Vygon, Aachen, Germany) and Statham

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transducers (Gould, Coventry, UK) was used to carry out urodynamic measurements. Intravesical, urethral and abdominal (rectal) pressures were recorded simultaneously and electronic subtraction was used to obtain detrusor pressure and urethral closure pressure. During UPP measurements the catheter was steadily withdrawn through the urethra at 0.7 cm/s at a constant bladder volume of 300 ml of physiological saline and with an infusion rate of 5 ml/min. The same procedure was carried out with the women coughing repeatedly to obtain a urethral closure pressure profile. If a positive area remained under the curve, the test was considered normal. This would be the expected profile of a continent patient. If pressure equalisation occurred throughout the entire closure pressure profile, the test was deemed abnormal (Fig.). This abnormal profile has been considered pathognomonic of patients with GSI (Richardson, 1986). Methods, definitions and units conform to the standards recommended by the International Continence Society (Abrams *et al.*, 1988) except where specifically noted.

Sensitivity, specificity and the predictive value of the normal and abnormal test were calculated by standard 2 × 2 tables (Stempel, 1982).

Results

The clinical stress test revealed 2 groups of patients: no incontinence was demonstrable in 320 subjects (33%; mean age 49.3 ± 1.3 years) and GSI was confirmed in 661 patients (67%; mean age 53.4 ± 1.2 years). The distribution of normal and abnormal stress urethral pressure profiles is presented in the Table. According to our data, the cough pressure profile in the sitting position has a sensitivity of 93.3% and a specificity of 82.5%. The predictive values of the normal and the abnormal tests were 85.7% and 91.7% respectively.

Discussion

The method of Brown and Wickham (1969) showed the UPP during stress to have a high sensitivity in

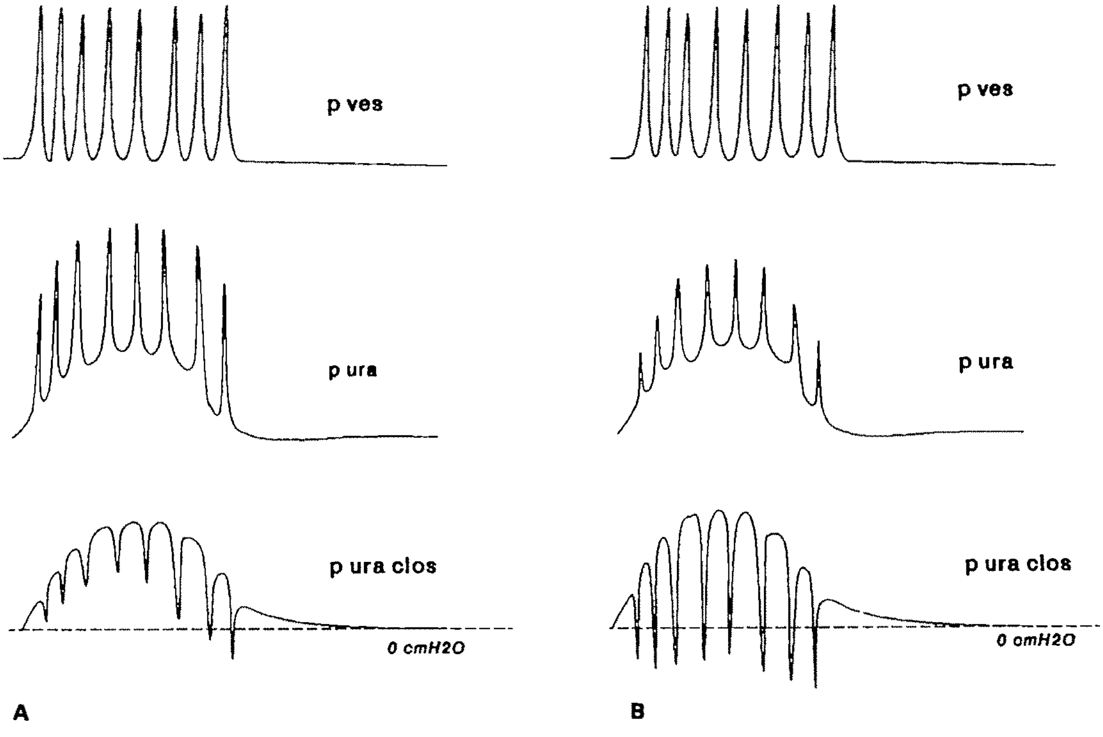

Fig. Demonstration of positive and negative urethral closure pressure profile along the whole length of the urethra. (A) A positive urethral closure pressure profile (p ura clos) is obtained when the urethral pressure (p ura) exceeds the intravesical pressure (p ves) during coughing. (B) Intravesical pressure (p ves) exceeds urethral pressure (p ura) during coughing, resulting in a negative urethral closure pressure profile (p ura clos).

Table Urodynamic Findings

	Clinical stress test		
	Positive (%)	*Negative (%)*	*Total (%)*
UPP clos negative	617 (93.3)	56 (17.5)	673 (68.6)
UPP clos positive	44 (6.7)	264 (82.5)	308 (31.4)
Total	661 (100.0)	320 (100.0)	981 (100.0)

UPP clos = Urethral closure pressure profile.

the diagnosis of patients with GSI. However, tonometric measurements of the urethra do not act as the "gold standard" but should be included in the range of diagnostic tests when assessing GSI. Problems arising during UPP measurements during stress are partly artefactual and due either to inaccurate techniques or marked genital prolapse (Schüssler, 1987; Versi, 1990). Erroneous results may be produced by catheter movement during coughing or when the urethra is significantly curved. The latter is found when microtip transducers are used and can be avoided by application of perfusion systems or by placing a microtip transducer inside a water filled balloon (Lose *et al.*, 1990).

Although both methods are acceptable in the standardisation of urinary tract function, the relative benefits of microtip and open catheters have led to controversy (Abrams *et al.*, 1978; Anderson *et al.*, 1983). The most significant error in the routine measurement of urethral pressure by the Brown and Wickham method is caused by the slow response of the system to increasing pressure (Abrams *et al.*, 1988).

Classification of the urethral closure pressure during stress as either positive or negative is a simple evaluation, but its high sensitivity and specificity make it suitable for assessing the majority of patients with GSI. On the other hand, it is difficult and time-consuming for a urodynamicist to measure all UPP variables in every woman. Moreover, Versi (1990) measured significant differences in UPP variables between normal women and those with GSI. However, the same author observed a large overlap in the measurements in these groups. Compared with pad tests, UPP measurements during stress seem to be a more reliable indicator of GSI. The lower sensitivity of pad tests (73–88%) (Jorgensen *et al.*, 1987; Kralj, 1989) has encouraged the use of this urodynamic procedure in the differential diagnosis of female urinary incontinence. The advantages of continuing to use the cough profile are its high sensitivity and specificity and the ease with which it can be performed at the same time as other urodynamic tests.

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Colonoscopic Control of Uretero-enteric Anastomoses in Internal Urinary Diversion

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Summary—Twenty-four patients with internal urinary diversion following total bladder ablation underwent colonoscopic control of the uretero-enteric anastomoses. The techniques performed were: rectal bladder with colostomy according to Mauclaire (11 patients); rectal bladder with abdomino-perineal pull-through according to Heitz-Boyer/Hovelacque (6); ureterosigmoidostomy (7). The uretero-enteric anastomoses were divided into 3 categories according to the colonoscopic appearance: "nipple-like", nearly flat and flat anastomosis. Urographic examinations were carried out in all patients and the results demonstrated that the "nipple-like" anastomosis was the most successful for the preservation of upper urinary tract integrity.

One of the outstanding problems of urinary diversion is the ureteric anastomosis. Many surgical techniques have been used but the results remain controversial and none of the techniques can be considered as the most reliable.

Surveillance colonoscopy is a standard technique performed in the out-patient department for the early detection of malignancy (Rossini *et al.*, 1979; Uehling *et al.*, 1982). This technique can be used to check the site of ureterocolic anastomoses and thus indicate the integrity of the upper urinary tract before serious renal impairment develops. At this institution, uretero-enteric anastomoses following bladder ablation for tumours or exstrophy are carried out by direct non-tunnelled intubation. Surveillance fibreoptic colonoscopy was performed in 24 patients with internal urinary diversion and the findings were compared with radiological ones (IVU: intravenous urography).

Patients and Methods

Eleven patients had a rectal bladder and colostomy according to Mauclaire's procedure (Bracci, 1964); 6 had a rectal bladder and abdomino-perineal pull-through (Heitz-Boyer and Hovelacque, 1912); 7 had a ureterosigmoidostomy. All of the anastomoses were carried out by the same surgical team with insertion of 3.5 to 4 cm of the ureter into the rectum through an incision in its antero-lateral wall, fixing the lower edge with a stitch (Bracci, 1967, 1968) (Fig. 1). IVU and colonoscopic evaluations were performed 3 to 10 years after operation. A 3-year interval is considered necessary to achieve complete tissue healing and facilitate evaluation of the anastomotic site.

Results

Three different types of ureteric anastomosis were found in the 24 patients:

Type I (nipple anastomosis): a nipple-like bulge protruding from the rectal mucosa.

Type II (nearly flat anastomosis): slightly protruding from the rectal mucosa.

Type III (flat anastomosis): flat rectal mucosa showing a mild depression at the anastomotic site.

Table 1 summarises the results of this study and compares the operations performed with the endoscopic viewings. In Table 2, anastomotic features are compared with the IVU findings.

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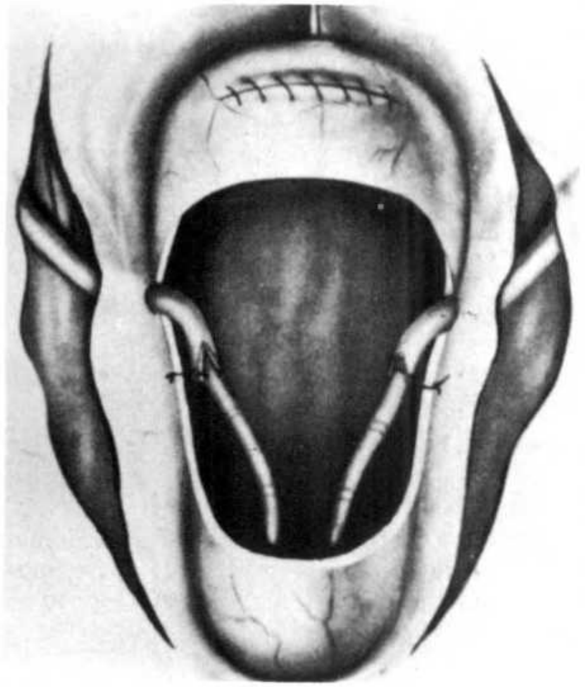

Fig. 1 Technique of ureteric intubation.

Discussion

The increasing number of bladder tumours has led to extensive surgical techniques demanding an internal continent urinary diversion and the problem of uretero-enteric anastomosis has therefore assumed great importance. Surveillance colonoscopy was carried out periodically to check the anastomotic site, unanimously considered to be at risk of colonic cancer (Berg *et al.*, 1987). Apart from the onset of neoplasia, there has also been radiological evidence that the urinary tract proximal to the ureteric anastomosis may undergo marked dilatation with severe renal impairment. In this respect, surveillance colonoscopy can predict renal impairment prior to radiological confirmation. In the present series, "nipple-like" anastomotic sites were associated with non-dilated upper urinary tracts, whereas 92% of the "flat" anastomotic sites were often associated with serious renal impairment. Type II anastomoses also showed a high failure rate, with dilatation in 78% and obstruction in 14%, although the radiological appearances were less severe than in type III.

A flat appearance implies fibrotic retraction of the anastomosis itself, leading to distal ureteric stenosis with reduced urine outflow (Figs 2, 3, 4). It can therefore be concluded that type I anastomosis is the best, and it also allows retrograde catheterisation.

In this series the ureteric anastomoses were all done in the same way by the same experienced surgical team: nevertheless, the colonoscopic findings fell into 3 groups, apparently at random. The explanation for this is far from clear and might depend on factors such as the vascular supply of the distal ureter or on the extent of surgical dissection. The surgical methods used in each case should be taken into consideration. In our experience the best colonoscopic viewings were found in

Table 1 Operations performed and Anastomotic Endoscopic Viewings

Operation	*No. of patients*	*No. of anastomoses checked*	*Type I*	*(%)*	*Type II*	*(%)*	*Type III*	*(%)*
MAUCL	11	22	17	(77)	2	(9.5)	3	(13.5)
USS	6	12	8	(66)	4	(34)	—	(0)
HBH	7	14	7	(50)	5	(35)	2	(15)

MAUCL = Mauclair's diversion. USS = Ureterosigmoidostomy. HBH = Heitz-Boyer/Hovelacque rectal bladder.

Table 2 Anastomotic Features compared with IVU Findings

Type of anastomosis	*No. of anastomoses checked*	*Upper urinary tract dilatation (%)*	*No dilatation (%)*	*Urinary tract obstruction (%)*	*Catheterisation possible*
I	32	5	95	—	YES
II	11	78	8	14	NO
III	5	8	—	92	NO

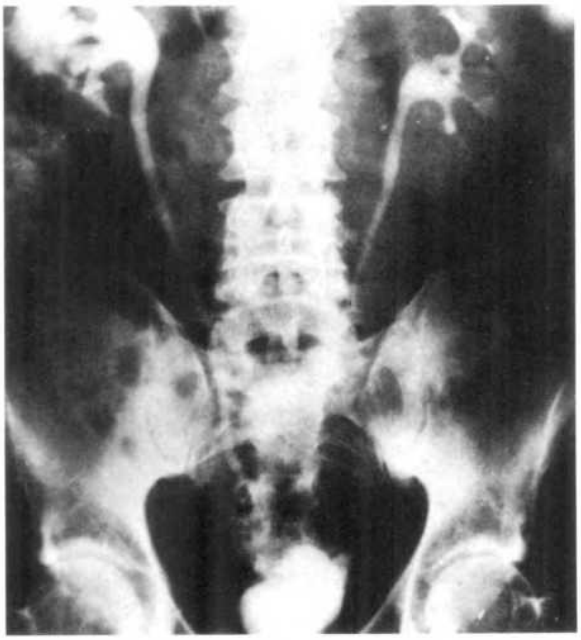

Fig. 2 IVU of patient with bilateral endoscopic viewing of type I uretero-enteric anastomosis: no dilatation of urinary tract.

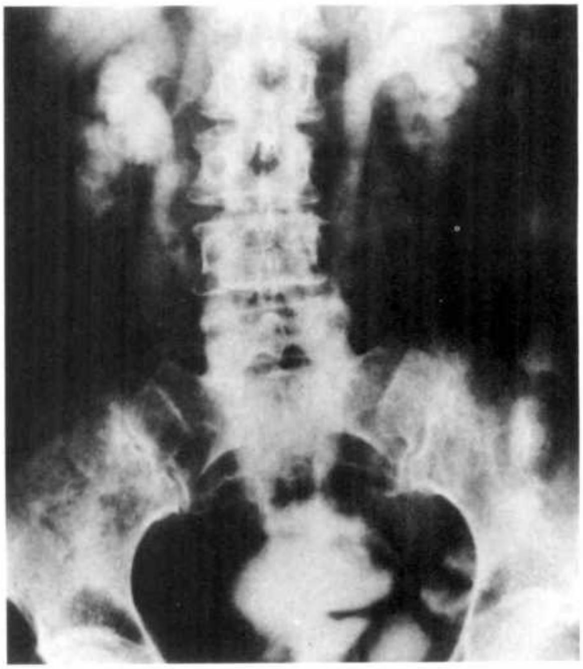

Fig. 4 IVU of patient with bilateral endoscopic viewing of type III anastomosis with marked bilateral obstruction.

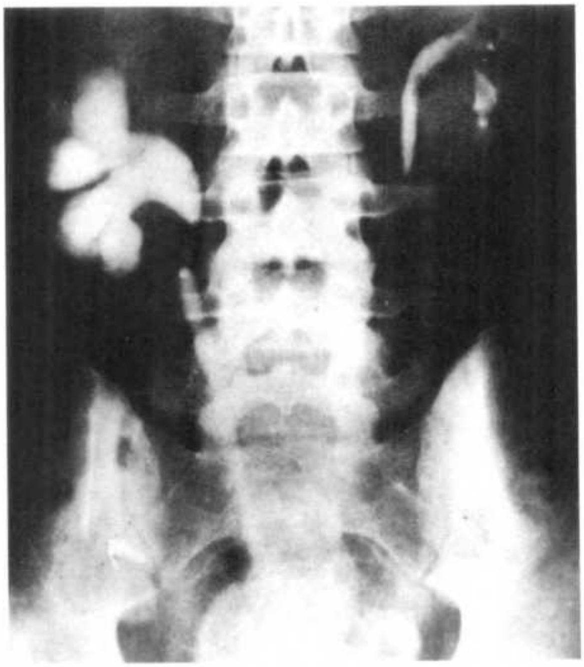

Fig. 3 IVU of patient with endoscopic viewing of type II anastomosis on the right and type I on the left: a mild degree of dilatation is visible on the right.

the patients undergoing Mauclaire's rectal bladder procedure. It is likely that in this operation there is lower endoluminal pressure leading to better ureteric control and less mixing of the faecal and urinary streams might explain the more favourable results (Bracci, 1975).

It is concluded that direct ureteric intubation is still a valid technique for urinary diversion, provided a length of at least 3.5 cm is used; this can avoid anastomotic retraction despite the predictable necrosis of the distal portion of the intubated ureter. Furthermore, when carrying out the anastomosis, attention should be paid to the vascular supply of the ureter because impaired blood flow might contribute to the changes which could be responsible for the colonoscopic appearance associated with impairment of upper urinary tract integrity.

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Role of Continent Suprapubic Diversion in Pelvic Cancer

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Summary—Seventeen patients with either current (n = 14) or previous (n = 3) pelvic malignant disease underwent continent urinary diversion using the Mitrofanoff principle in 16 and a Kock pouch in 1. Eight patients had bladder carcinoma, 6 had gynaecological malignancy, 2 had rectal cancers and 1 had a squamous cell carcinoma of the perineum. Fourteen underwent synchronous exenterative surgery and continent suprapubic diversion; plastic reconstructive procedures were required in 4. There were 2 post-operative deaths and 5 patients have developed further tumour recurrence. Continence was satisfactory in all patients with a median interval of intermittent self-catheterisation of 4 h.

The standard method of urinary diversion following cystectomy remains the ileal conduit. Alternatives to cutaneous diversion include the construction of a neobladder from an intestinal segment which is drained either via the urethra or via a continent suprapubic diversion. Inadequate emptying and enuresis, particularly at night, are not uncommon following anastomosis of such a neobladder to the urethra. After cystourethrectomy, continent suprapubic diversion is the only real alternative to an incontinent stoma and bag other than ureterosigmoidostomy with its widely acknowledged complications.

Various techniques of continent suprapubic diversion have been described. The principal methods depend either on the formation of a nipple valve (Kock, 1969), utilisation of the ileocaecal valve (Gilchrist *et al.*, 1950), or on the anti-refluxing implantation of a small calibre tube such as appendix into a urinary reservoir (Mitrofanoff, 1980).

This report details our experience of continent suprapubic diversion in patients with pelvic malignant disease using the Mitrofanoff principle.

Patients and Methods

Seventeen patients with a current or previous history of pelvic cancer underwent continent or suprapubic diversion. Their median age was 59 years (range 27–72) and the underlying pathology is summarised in Table 1.

They were selected from patients presenting with pelvic cancer who required radical surgery and were deemed physically and emotionally fit for major reconstruction. All were counselled preoperatively regarding the pros and cons of an incontinent versus a continent stoma. All were

Table 1 Underlying Pathology in Patients undergoing Continent Suprapubic Diversion

Pathology	*No. of patients*
Transitional cell carcinoma of bladder (T3, G3 in 4; extensive carcinoma *in situ* + superficial disease in 3)	7
Squamous cell carcinoma of the bladder	1
Carcinoma of cervix (Squamous cell in 3, adenosquamous in 1, adenocarcinoma in 1)	5
Adenocarcinoma of rectum	2
Adenocarcinoma of vagina	1
Squamous cell carcinoma of urethra	1

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extensively investigated and staged pre-operatively. This always included computed tomography, an assessment of renal function and an examination under anaesthesia (EUA). Where appropriate, pre-operative consultation was sought with gynaecological, plastic and/or general surgical teams and if necessary a combined EUA was performed.

Fourteen patients underwent continent suprapubic diversion and cancer-clearing surgery with curative intent concurrently. Four patients also underwent concurrent plastic reconstructive procedures including myocutaneous flap grafting and/or vaginoplasty. Details of the operations performed concurrently with continent suprapubic diversion are summarised in Table 2.

Eight patients underwent radical cystourethrectomy (7 for transitional cell and 1 for squamous cell carcinoma). Seven of them had a Mitrofanoff reconstruction and 1 underwent construction of a Kock pouch. Two women underwent synchronous anterior exenteration and a Mitrofanoff reconstruction for locally recurrent carcinoma of cervix. One woman with extensive intra-epithelial carcinoma of cervix who had previously had a hysterectomy, laser therapy and radiotherapy underwent vulvo-colpectomy and because of bladder involvement a cystectomy. Reconstruction was by means of a rectus abdominis flap, ileovaginoplasty and a Mitrofanoff procedure. Another woman with adenocarcinoma of the vagina who had persisting disease despite radiotherapy underwent hysterocolpectomy, urethrectomy and a partial cystectomy. The reconstruction included ureteric reimplantation, colovaginoplasty and a Mitrofanoff procedure in which appendix was implanted into the bladder remnant. A further woman had a local recurrence of a rectal carcinoma involving the vagina 2 years after abdominoperineal resection. This persisted despite radiotherapy and she therefore underwent a pelvic clearance, reconstruction being by means of a rectus flap, ileovaginoplasty and a Mitrofanoff procedure. A male patient with an ulcerating squamous cell carcinoma in the perineum underwent radical excision of the penis, urethra and perineal ulcer. Reconstruction included a rectus flap and a Mitrofanoff procedure.

A further 3 patients who had had previous treatment for pelvic malignancy underwent continent suprapubic diversion. All were reassessed and considered to be free of recurrent disease. In 2 women with cervical cancer, treatment had included external beam and intracavity radiotherapy. Both had been disease-free for 3 years but had developed severely contracted bladders, 1 with intractable incontinence and the other with bilateral ureteric obstruction. The third patient had undergone abdominoperineal resection for a rectal cancer 13 years previously. She had persistent urinary incontinence despite endoscopic and open colposuspensions.

The urinary reservoir was constructed from detubularised caecum and ascending colon in 13 patients. In each case the appendix was mobilised on its pedicle, reimplanted into the caecum and brought to the skin surface as previously described (Woodhouse *et al.*, 1989). In 3 patients bladder was available. In 2 of them ureter was used as a catheterisable conduit with an associated transuretero-ureterostomy as previously described (Woodhouse *et al.*, 1989). In the third patient appendix was implanted into the bladder and brought to the surface as a continent catheterisable vesicostomy. The seventeenth patient had a conventional Kock pouch.

Table 2 Operations performed concurrently with Continent Urinary Diversion and Details of Previous Surgery and Radiotherapy

	No. of patients
Bladder cancer	
Radical cystourethrectomy (pre-operative deep X-ray therapy in 1)	8
Other pelvic malignancy	
Anterior exenteration (previous deep X-ray therapy in 2, previous hysterectomy in 1)	2
Vulvo-colpectomy, cystectomy, rectus flap and ileo-vaginoplasty (previous hysterectomy and deep X-ray therapy)	1
Hystero-colpectomy, urethrectomy, partial cystectomy, ureteric reimplantation and colo-vaginoplasty (previous deep X-ray therapy)	1
Pelvic exenteration, rectus flap and ileo-vaginoplasty (previous A-P resection and deep X-ray therapy)	1
Radical excision of penis, urethra and perineal ulcer + rectus flap	1

Results

There were 2 post-operative deaths. In the patient who had excision of an ulcerating perineal tumour the rectus abdominis flap necrosed and this was replaced with a groin flap but this also failed. Renal and multi-organ failure followed. In the second patient an acute abdomen and signs of sepsis necessitated re-exploration 1 week after radical cystourethrectomy and a Mitrofanoff reconstruction. The patient had a fatal myocardial infarct after this operation. These 2 patients were the second and third oldest in the series.

The median follow-up in the remaining patients was 24 months (range 6–36). All of these patients achieved continence, though 1 required revision of the appendix conduit to do so. Patients self-catheterise at intervals of 4 to 5 h and occasionally at night. One patient required dilatation of an appendiceal conduit. Another had difficulty catheterising a ureteric conduit and ultimately required conversion to a Kock nipple. One patient had minor leakage in association with urinary infection which required more frequent catheterisation. A further patient who had received radiotherapy developed a stricture at the site of ureteric reimplantation into the neobladder. This was initially dilated percutaneously but ultimately required open revision because of upper tract deterioration. There were no other upper tract complications and no significant metabolic complications were encountered.

Tumour recurrence has occurred in 5 patients. Three are alive with distant metastases which presented 5, 6 and 17 months following radical cystourethrectomy for bladder cancer (squamous cell in 1 and transitional cell in 2). The women with cervical and vaginal carcinoma respectively developed local recurrence 8 and 6 months after combined exenterative surgery and reconstruction. Both underwent further extensive pelvic surgery with reconstruction of a neobladder in 1. The continent diversion was preserved in both, but they died from widespread disease at 12 and 16 months respectively. One of these women presented with difficulty in self-catheterisation which was found to be due to tumour recurrence around the Mitrofanoff appendix.

Discussion

Although the ileal conduit remains the standard method of urinary diversion after cystectomy and other ablative pelvic operations, efforts to avoid a wet stoma and bag have been intensified in recent years. Camey and Le Duc (1979) first popularised anastomosing an intestinal neobladder to the urethra and numerous variations on this theme have followed. These procedures are not uncommonly complicated by inadequate emptying and enuresis, particularly at night, necessitating intermittent self-catheterisation and in some cases an artificial sphincter. After cystectomy, therefore, continent suprapubic diversion (particularly with a discrete stoma) is an attractive alternative to procedures in which a neobladder is anastomosed to the urethra. Following cystourethrectomy and other procedures which remove or destroy the continence mechanisms, continent suprapubic diversion is in our view the only realistic alternative to an incontinent stoma.

Skinner *et al.* (1987) have popularised the use of the Kock pouch after radical cystourethrectomy. However, we have not found the Kock pouch easy to construct and even in the hands of enthusiasts there is a significant rate of revisional surgery (Cumming *et al.*, 1987). We have previously reported our early experience of continent suprapubic diversion employing the Mitrofanoff principle in younger patients who had originally undergone urinary diversion in childhood (Woodhouse *et al.*, 1989). In some of these patients native bladder was available, but following cystectomy we have found detubularised caecum and ascending colon to be the most satisfactory arrangement for the reservoir with appendix as the catheterisable conduit.

The present series comprised a relatively high risk group of patients in so far as 6 of them had had previous radiotherapy and/or previous primary surgical treatment for their underlying disease (Table 2). The combination of a radical pelvic cancer exenteration with a concurrent complex reconstruction of a continent suprapubic diversion in an older, less fit patient is a different prospect from performing this type of diversion alone in an otherwise healthy young adult. In the younger group we have now performed over 40 continent diversions with no mortality. Of the 2 deaths in this series 1 resulted from failed plastic surgical reconstruction in the patient with a fungating perineal squamous cell tumour. The second death, however, emphasises the increased risks of performing this type of reconstruction concurrent with radical cystourethrectomy for bladder cancer. This patient did have evidence of cardiovascular disease preoperatively and was therefore a relatively high risk. We are now more critical in evaluating patients pre-operatively and in those patients keen to avoid a bag but considered unfit for a synchronous continent diversion we offer to construct a colon conduit with the option of a later conversion to a continent suprapubic diversion.

Women with cervical cancer constituted the second largest group in the present series. Patients with central recurrences and no evidence of distant disease following previous radiotherapy are offered anterior exenteration with the possibility of a continent suprapubic diversion. If there is any evidence of pelvic sidewall or iliac or para-aortic lymph node involvement on per-operative frozen section, an ileal conduit is constructed instead of the more complicated procedure.

Continent suprapubic diversion also has a place in the reconstruction of the lower urinary tract in patients who have radiation damage following previous treatment of pelvic cancers, as in 2 of the women with cervical cancer in the present series. In some of these patients substitution cystoplasty may be feasible. However, in those with sphincteric damage and in those with severe radiation fibrosis, continent suprapubic diversion may be preferable.

Two patients in this series had colostomies. We do not regard this as a contraindication to continent urinary diversion. Many patients prefer to have 1 bag rather than 2.

Continent urinary diversion has a wide range of application in patients with pelvic malignant disease. We prefer the Mitrofanoff method of reconstruction. In the elderly, less fit patient typical of those requiring cystectomy for bladder cancer, great care must be taken in selection as the concurrent construction of a continent suprapubic diversion confers additional risks on an already major procedure.

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Carcinoma *in situ* as a Prognostic Factor for G3pT1 Bladder Tumours

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Summary—G3pT1 bladder cancer has traditionally been regarded as a superficial tumour with a high risk of progression. We have studied 37 patients with initial G3pT1 bladder tumours treated between January 1981 and December 1985. They were divided into 2 groups according to the association with carcinoma *in situ* (Cis) at the time of diagnosis.

Clinical behaviour was analysed at 5 years. The first group (without Cis) showed progression and recurrence rates similar to those of low grade, low stage bladder tumours. The second group (with Cis) had a similar rate of recurrence but their progression rate was 65%.

High grade bladder tumours which invade the submucosa show high rates of recurrence and progression (Jakse *et al.*, 1987; Birch and Marland, 1989; Jenkins *et al.*, 1989) and are closely associated with carcinoma *in situ* in 38% of cases (Vicente *et al.*, 1987). If there is a common origin of both entities perhaps the G3 transitional tumour is the intraluminal expression of carcinoma *in situ* (Algaba, 1987). The high index of progression of Cis, from 60 to 80% within 5 years (Birch and Harland, 1989), may indicate that there is an association between both entities which can worsen the prognosis.

We have compared the clinical behaviour of G3pT1 transitional tumours associated with Cis with those which were not, in order to establish a high risk group within the high grade transitional bladder tumours.

Patients and Methods

From 1 January 1981 to 31 December 1985, 558 initial transitional bladder tumours were treated in this clinic; from this group we selected the 37 patients with G3pT1 tumours.

In all cases, randomised biopsy of the trigone, posterior wall, right and left lateral walls and the bladder dome was carried out at the time of tumour resection. Cold biopsy of the prostatic urethra has been included since 1982.

Two groups were established according to the presence or absence of carcinoma *in situ* at the time of diagnosis.

Group I consisted of 20 patients who proved to have G3pT1 transitional cell carcinoma of the bladder with negative random biopsies. Included in the group were 2 females and 18 males with a mean age of 68 years (range 47–83). Mean follow-up was 51.5 months (range 3–96). Half of these patients were treated with intravesical chemotherapy (doxorubicin, thiotepa).

Group II consisted of 17 patients with G3pT1 bladder transitional cell carcinoma associated with Cis. It included 1 female and 16 males with a mean age of 64 years (range 45–85). There was a mean follow-up of 50.9 months (range 6–76). Fifteen patients received intravesical treatment (BCG, mitomycin) or systemic treatment with cyclophosphamide.

Follow-up of all patients continued until death or for a minimum period of 5 years.

Check cystoscopy and cytology were performed every 4 months for the first 2 years and twice a year thereafter. Transurethral resection (TUR) and randomised biopsy were carried out when a tumour recurred. Where Cis persisted or the tumour

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progressed after chemotherapy, radical cystectomy was performed.

Results

In Group I, 14/20 patients had recurrent tumours (mean number of recurrences 2.07 per patient) (Fig. 1). Only 2 patients developed Cis in association with a recurrence. Intravesical chemotherapy did not prevent recurrences in 9 of 10 patients. The mean tumour-free period was 12.6 months (range 4–28).

Two cystectomies were carried out: the first was for fibrosis of the bladder secondary to multiple recurrent TURs and the second for tumour recurrence associated with Cis.

Only 2 patients developed tumour progression (Fig. 2); 1 died after muscle invasion at 18 months and the other developed an upper tract recurrence and died 12 months after diagnosis. A third patient died of an acute heart attack at 3 months.

At 5 years, 60% of patients were still alive with superficial disease and 23% were alive and tumour-free (Fig. 3).

In Group II, Cis was multifocal in 13 of 17 patients, with a mean of 3 positive biopsy sites. Two patients were treated with immediate cystectomy following diagnosis.

Of the other 15 patients, 14 developed recurrences on 1 to 5 occasions (mean 1.9 per patient); in 9 cases biopsy revealed further Cis in the posterior wall. The mean time free of disease was 14.6 months.

The tumour progressed to muscle invasion in 11 cases (Fig. 2) and 10 of these patients underwent cystectomy. In 1 patient cystectomy was not carried out because of age and the degree of anaesthetic risk. Four patients underwent pre-operative radiotherapy before planned cystectomy. Three patients were treated with systemic chemotherapy after radical surgery. Cis was found in 9 of the 12 patients treated by cystectomy. Ten patients (Fig. 3) died as a result of progression of disease, after a mean of 33.9 months (range 6–72) from diagnosis.

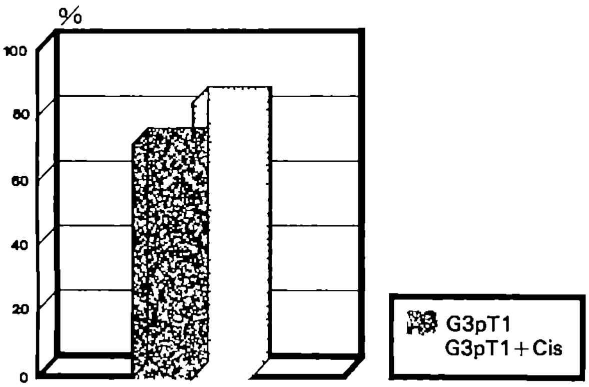

Fig. 1 Recurrence rate in both groups.

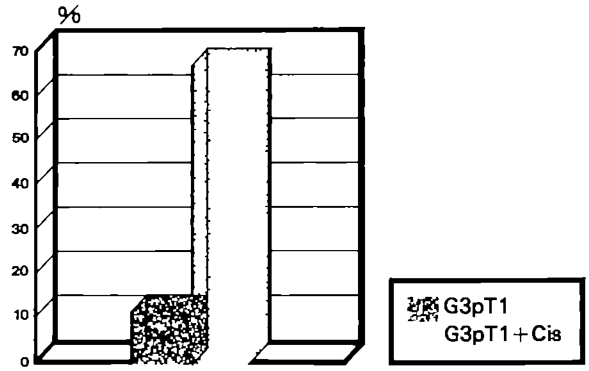

Fig. 2 Progression rate in both groups

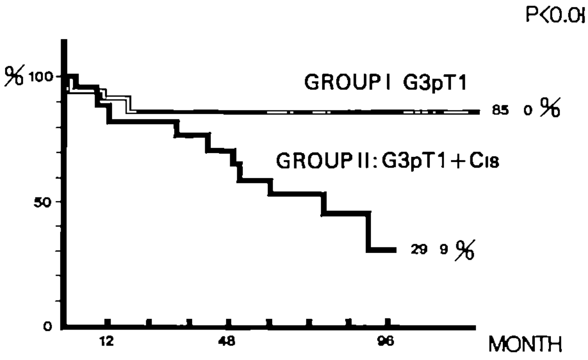

Fig. 3 Kaplan and Meier survival curves at 5 years

After 5 years, 2 patients were alive with progressive disease and 3 were alive and well after 61.6 months.

Discussion

In our experience, the G3pT1 superficial transitional bladder tumour accounts for 6.6% of initial bladder cancers. It is concomitant with Cis in 46% of cases. In view of the poor prognosis of Cis (Heney *et al.*, 1982) and its high progression index (Birch and Harland, 1989), the association between G3pT1 and Cis merits the systematic use of random biopsies of non-tumour-bearing urothelium (Algaba, 1987; Vicente *et al.*, 1987). The need for random biopsies is even more evident when the clinical behaviour of G3pT1 is analysed.

The main difference between groups I and II is not in the recurrence rates, which are higher than for low grade superficial tumours (Jakse *et al.*, 1987; Birch and Harland, 1989) and are not significantly different between groups I and II, but in the rates of progression. While only 10% of G3pT1 tumours not accompanied by Cis progressed within 5 years, 64% of G3pT1 tumours associated with Cis became muscle-invasive tumours. Survival after 5 years was 83% and 30% for groups I and II respectively.

In the present series, only 14% of patients with G3pT1 tumours without Cis went on develop Cis later, which may support the theory that isolated G3pT1 behaves like a superficial tumour as far as progression is concerned. Although the recurrence rate may be higher, these patients can be treated similarly to those with superficial low grade tumours.

Patients in the second group, whose G3pT1 tumours were associated with Cis, developed extremely aggressive tumours within 3 years. Different treatment is required for these patients.

Intravesical chemotherapy does not appear to produce satisfactory results (Winkler *et al.*, 1990). Radical radiotherapy may improve results (Birch and Harland, 1989; Jenkins *et al.*, 1989). Immunochemotherapy with BCG requires strict supervision, and cystectomy may be a more satisfactory approach if disease persists 6 to 8 months from diagnosis (Birch and Harland, 1989; Winkler *et al.*, 1990).

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Histopathology of Benign Prostatic Hyperplasia after Failure of Hyperthermia Treatment

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Summary—We have used a fine morphometric method to evaluate hyperplastic prostate tissue after treatment by local hyperthermia and compare it with untreated specimens. Local hyperthermia was delivered to the prostate gland by a transrectal applicator using microwaves at 915 MHz. Prostatic tissue was obtained from 13 patients who had completed a course of local hyperthermia treatment and who underwent prostatectomy 3 to 12 months later because the treatment had failed. Prostatic tissue from 9 patients who had undergone prostatectomy with no previous treatment served as a control. A significant reduction in the volume fraction of fibrous tissue was found in the study group (37%) compared with the general population (48%). No inter-group difference was observed in the volume fractions of vascular or glandular tissue. We suggest that the difference observed in the fibrous elements may be the reason for the failure of treatment and that the histological composition of the diseased gland may, therefore, be a key factor in determining the outcome.

The effect of hyperthermia on neoplastic tissue in culture and in experimental animals is the selective destruction of malignant cells with minimal damage to normal cells (Cavaliere *et al.*, 1967). Local hyperthermia applied to the normal canine prostate *in vivo* demonstrated that heat invariably caused mononuclear inflammatory infiltration in the interstitium and polymorphonuclear infiltration in glandular elements (Leib *et al.*, 1986). When local hyperthermia was used to treat 20 patients with prostatic cancer, distinct hyperaemic changes were noted 1 week after treatment, consisting of diffuse oedema with interstitial lymphoplasmatic cellular infiltration (Strohmaier *et al.*, unpublished data). In some patients vacuolation of tumour cell nuclei and nucleolar loss were found. Local hyperthermia is currently being used to treat benign prostatic hyperplasia (BPH) on a limited experimental basis. Preliminary reports are encouraging but no information has yet been obtained as to the mechanism of action (Servadio *et al.*, 1989).

Studies of the tissue changes in the human prostate reacting to heat have shown that light and electron microscopy of prostatic specimens are not discriminative. Bartsch *et al.* (1979a, b) reported that morphometric methods could be used to study both the normal and the hyperplastic prostate gland, demonstrating fine tissue and cell changes. We have recently adapted this methodology to achieve a finer degree of resolution than that previously attained (Siegel *et al.*, 1990) and we used it to evaluate hyperplastic prostate tissue after treatment by local hyperthermia and compare it with untreated specimens.

Patients and Methods

Local hyperthermia was delivered to the prostate gland by the Prostathermer (Tm) model 99-D using microwaves at 915 MHz. With this system an applicator is introduced into the rectum and positioned at the level of the prostate while a specially adapted 18 F urinary catheter with temperature-measuring probes is inserted into the bladder. Maximum prostatic temperature is calcu-

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lated continuously throughout the treatment; its estimation is based on temperatures in the rectum and prostatic urethra. Treatment was given on an out-patient basis using local anaesthesia for the insertion of the urethral catheter. The prostate was heated to 42 ± 1.5°C during each treatment session, which lasted 1 h.

The diagnosis of benign prostatic hypertrophy was established by 2 independent urologists, and only patients requiring surgery by conventional standards were candidates for local hyperthermia. To achieve an objective assessment of the results a scoring system was used which took into account peak urine flow and residual urine. Subjective criteria were assessed by means of an elaborate questionnaire completed by patients prior to treatment and at 1-, 3- and 6-month follow-up visits. Based on these criteria, patients were diagnosed as either successfully responding to treatment, thus remaining in the follow-up group, or as treatment failures and scheduled for surgery.

Prostatic tissue was obtained from 13 patients who had completed a full course of local hyperthermia and who underwent prostatectomy 3 to 12 months later following failure of the treatment. Prostatic tissue from 9 patients who underwent prostatectomy with no previous treatment served as a control. The 2 groups were closely matched with respect to age, type of surgery and weight of the resected gland (Table 1).

Specimens were weighed and examined as to texture, shape and colour. The specimens were then paraffin-embedded and sections 6 μm thick were stained using standard haematoxylin and eosin techniques. The entire tissue was submitted to microscopic examination. No evidence of carcinoma was noted. The pathologist confirmed benign prostatic hyperplasia in all cases.

Morphometric evaluations were performed at a magnification level of × 400. The volume fraction of the following tissue components was determined using a morphometric approach: interstitial fibrous tissue, Vv_{FB}; muscle cells, Vv_{MS}; glandular cells, Vv_{GL}; vascular tissue, Vv_{VS}. The volume fractions of fibrous tissue, muscles, glandular cells and vascular tissue were related to the unit volume of prostatic tissue and were determined according to the equation:

$$Vv_i = \Sigma Pi/\Sigma Pt_i$$

Where i is the tissue component under consideration, Vv is its volume fraction, Pi is the number of test points in the test system associated with i, and Pt_i is the number of points in the test system. The volume fraction (Vv_i) was estimated from the areas as determined by point counting using a coherent multi-purpose test grid with a test line of 1.5 cm. At least 20 systematic test areas were analysed for each tissue component in a specimen (80 test areas), and T test statistical analysis was performed.

Table 1 Study and Control Groups

	Study group	*Control group*
No. of patients	13	9
Mean age (years)	71 ± 8.1	73 ± 6
Transurethral resection	8	7
Suprapubic prostatectomy	5	2
Weight of resected prostate (g)	33 ± 24	27 ± 20

Results

The volume fractions of the glandular, fibrous, muscular and vascular components in patients who failed to respond to hyperthermia treatment and in the control group are summarised in Table 2.

A significant reduction in the volume fraction of the fibrous tissue was found in the study group compared with controls, as was a significant increase in the volume fraction occupied by muscle cells. There was no inter-group difference in the volume fractions of the vascular and glandular tissue.

Discussion

The prostate gland is a heterogeneous structure which includes glandular and fibromuscular tissue. Although the basic anatomy can be identified throughout life, considerable morphological change is associated with the development of the mature structure in response to the stimulus of androgenic hormones and, later in life, as a result of focal atrophy and involvement in benign hyperplastic change (Blacklock, 1981).

Table 2 Volume Fractions of Tissue Components Calculated as % of Total Tissue Volume

Component	*Control group (n=9) (%)*	*Hyperthermia failure group (n=13) (%)*
Fibrous	46.85 ± 0.98	*37.07 ± 0.72
Muscle	7.17 ± 0.32	*14.55 ± 0.39
Vascular	3.04 ± 0.17	3.11 ± 0.14
Glandular	18.77 ± 0.54	18.62 ± 0.45

* $P < 0.001$.

Quantitative morphometric analysis provides information on the relative volume of various components of the prostate in different states. Such a methodology provides objective and reproducible values for any morphological structure and thus allows statistical comparisons. We have modified the original morphometric approach of Bartsch *et al.* (1979a, b) to facilitate the resolution of the stromal portion of the human prostate into its fibrous, muscular and vascular components (Siegel *et al.*, 1990). It is interesting to note that if one compares the volume fraction of the stroma as a whole between the 2 groups there is no difference: 55% in the study group and 57% in the controls. Only the breakdown of the stroma into its various sub-components demonstrates the differences between the groups.

Local hyperthermia is currently being used to treat BPH on a limited experimental basis. Preliminary reports are encouraging but no information has yet been obtained as to the mechanism of action (Lindner *et al.*, 1987, 1989). We have demonstrated the effectiveness of local hyperthermia in alleviating the urinary outflow obstruction associated with BPH while avoiding surgery and its concomitant post-operative complications (Lindner *et al.*, 1987, 1989, 1990).

Given the random selection of patients to the hyperthermia group, it might be assumed that at the outset of the study the various tissue components evaluated occupied the same volume fractions in all patients. If so, the differences observed after treatment would represent the effect of hyperthermia. On the other hand, since one cannot anticipate an increase in muscular elements in response to this treatment, it is possible that patients become responders or non-responders to hyperthermia on the basis of the morphology of the BPH. In that case, what we observe here are morphological characteristics of the population predisposed to treatment failure. In the absence of more detailed knowledge of the effect of hyperthermia on tissue, other interpretations of the data are possible. It is important to remember that since the study could be performed only on prostate specimens after prostatectomy, no tissue was available from patients who responded to hyperthermia treatment and were thereby spared the need for surgical intervention.

The glandular element appears to play no part in this phenomenon. Conversely, the non-glandular tissue of the prostate appears to be heat-sensitive. Included in this component are the pre-prostatic sphincter, the anterior fibromuscular stroma and the prostatic capsule, the nerve and vascular supplies. The pre-prostatic sphincter has a resting tone which maintains closure of the proximal urethral segment in the normal prostate, but which in the hyperplastic prostate may become obstructive. The anterior fibromuscular stroma in the normal prostate is composed of large compact bundles of smooth muscle cells randomly orientated and separated in some areas by bands of fibrous tissue. In pathological processes the morphology of the prostate gland begins to deviate from the normal. A variety of histological changes may be expressed, such as post-inflammatory atrophy, cystic atrophy, focal proliferation of stroma, newly formed duct-acinar structures, or a combination of all of these changes. Morphological changes due to ageing are characteristically diffuse, but foci of atrophy, inflammation or cystic changes may be present (McNeal, 1988). How heat influences each of these components is difficult to evaluate, but it is possible that each component reacts differently.

The objective in treating BPH with hyperthermia is to alleviate the symptoms of urinary obstruction without tissue destruction. It is not yet clear whether heating the obstructive tissue alone is more beneficial than heating the entire prostate. However, in our experience with hyperthermia, a 40% success rate was achieved in the relief of urinary retention after 1 year's follow-up (Lindner *et al.*, 1987, 1989); a 60% success rate, as assessed by improved uroflowmetry, residual volume and symptomatic relief over a 3-year period following local hyperthermia, has been achieved. However, no change was observed in the volume of the glands as estimated by ultrasound (unpublished data). Thus it is possible that a change in the fibrous elements which constrict the stromal supporting structure of the entire gland is responsible for a change in the tissue tone, and hence relief of symptoms.

In the present study the general BPH population was compared with a study population (patients who failed to respond to hyperthermia) using a fine morphometric method. It was demonstrated that a lower volume fraction of fibrous elements (37%) was found in the study population than in the general population (48%). It is possible that this difference in the proportion of fibrous elements is the reason for failure of treatment and that the favourable gland histology consists of a high proportion of fibrous elements; other explanations may also exist.

If we can achieve a better understanding of the effect of heat on various tissue components we may pre-select a favourable population of patients for hyperthermia treatment, based on histology, and it will be possible to provide more effective treatment with a higher success rate.

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Late Complications of Prostakath Treatment for Benign Prostatic Hypertrophy

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Summary—The self-retaining intra-urethral device "Prostakath" was inserted in a consecutive series of 29 men with obstructive benign prostatic hypertrophy.

Fifteen patients were relieved of prostatic symptoms for an observation period of 22 weeks (range 2–60). The spiral was removed in 14 cases (48%) at an average of 14 weeks (range 1–82) after insertion; in 9 patients this was because of urinary retention and in 5 it followed dislocation of the stent into the bladder. Five stents removed after 44 weeks of treatment (range 21–82) were severely calcified. Light microscopic investigation of the Spirals that were removed revealed no damage to the gold-plated surface. All patients with calcification had chronic urinary infection resistant to antibiotic treatment. We believe that infected urine is the major factor responsible for the calcification. We suggest that patients with recurrent urinary infection after insertion of the Prostakath should be closely followed up and checked for stone formation by a plain X-ray of the bladder region. It may be advisable to change the Prostakath in patients with resistant urinary tract infection at 6-monthly intervals.

Long-term catheterisation has been the treatment of choice in patients with infravesical obstruction caused by benign prostatic hypertrophy (BPH) who are unfit for surgery. Since Fabian (1980) introduced the intraprostatic stent it has been possible to offer an alternative non-surgical treatment of BPH. Initial experience with the modified Danish spiral (Prostakath) has been promising when compared with permanent catheter treatment (Nordling *et al.*, 1989; Harrison and De Souza 1990; Nielsen *et al.*, 1990; Yachia *et al.*, 1990.

We report a late and probably rare complication of the new intraprostatic device: stone formation on the stent.

Patients and Methods

A consecutive series of 29 patients with BPH were treated by insertion of the Prostakath spiral. The median age was 80 years (range 62–95). Nineteen patients were unfit for surgery and regarded as candidates for permanent catheterisation rather than transurethral resection of the prostate (TURP). Four patients were senile and Prostakath treatment was initiated because they had constantly removed the urethral balloon catheter. The last 6 patients requested the Prostakath instead of TURP.

The Prostakath is a gold-plated spiral of steel with an outer diameter of 21 F. The gold surface has a high degree of biocompatibility with the urothelium of the urethra. The spiral is mounted on a catheter/stent by which the device can be positioned in the prostatic part of the urethra. The distal part of the spiral has a "neck" for the sphincter area. In the bulbar part of the urethra a small coil of the Prostakath secures it in position (Nordling *et al.*, 1989).

It was possible by suprapubic ultrasonic scanning through a full bladder to estimate the length of the prostatic part of the urethra. We selected a spiral 10 mm longer than the length of the prostatic urethra and under local anaesthesia a 7 F ureteric catheter was inserted transurethrally into the bladder. This catheter served as a guidewire for the

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Prostakath, which was inserted and positioned under ultrasound guidance. We then asked the patients first to cough and then to pass urine, in order to establish the position of the Prostakath. The results of this test and of observation of the micturition pattern during the next 24 h were used to decide whether endoscopic adjustment of the spiral was indicated. Before discharge we performed flowmetry and estimated the volume of residual urine by ultrasound. Ampicillin 2 g was given intravenously as prophylaxis immediately before inserting the stent.

The patients were followed up in the out-patient clinic by flowmetry and urine specimens for culture after 1 week, after 4 weeks, and thereafter every 3 months. Median follow-up for this study was 18 weeks range (2–82).

Results

Nineteen men with total urinary retention due to BPH had a permanent urethral catheter before being offered the Prostakath. In 7 of the remaining 10 patients the median maximum urinary flow rate was 7 ml/s (range 4–10) before insertion of the Prostakath. Fifteen patients were relieved of prostatic symptoms, with a median maximum flow rate of 12 ml/s (range 7–35) during 22 weeks' follow up (range 2–60). Ultrasound scanning revealed that residual urine decreased on average from 735 ml to 36 ml in these 15 patients. During the first few days after insertion of the intraprostatic device it was necessary to perform urethroscopic adjustment of the spiral under local anaesthesia in 11 patients.

In 14 patients (48%) the spiral was removed after approximately 14 weeks (range 1–82): in 5 cases the stent was dislocated into the bladder and a further 4 developed urinary retention; in the remaining 5 patients calcification of the stent caused urinary retention as well as dysuria, haematuria and pain in the bladder region. The spiral was removed transurethrally in 12 patients, but in 2 men with severe calcification open surgery was necessary. The BPH was treated in 10 patients by TURP and in 1 by digital enucleation of the adenomas according to Freyer. Two patients had a permanent catheter and the last patient could pass urine freely after removal of the Prostakath.

The 4 senile patients were successfully treated with the Prostakath spiral and followed up for 12 weeks. Their incontinence was treated by a pad regime.

Twenty men (69%) had a chronic urinary infection before insertion of the Prostakath and 4 of them developed calcification on the stent. The last patient with stone formation on the Prostakath had sterile urine before starting treatment. All 5 patients with this late complication had recurrent urinary infection resistant to antibiotics during the observation period; urine culture showed 5 different species of bacteria. We diagnosed calcification of the stent by a plain X-ray of the bladder region (Fig.) 44 weeks (median) after starting treatment (range 21–82).

The 14 spirals that were removed, including those with stone formation, were examined by light microscopy for damage and defects on the surface, the encrustation having been dissolved in an acid solution. All of the spirals had an intact gold-plated surface and we could not identify any difference between the spirals removed because of calcification and those removed for other reasons.

Discussion

The currently accepted treatment of symptomatic BPH is TURP (Lepor, 1989) and it seems unlikely that pharmacological therapy in the immediate future will provide a reduction in the dynamic and static component of BPH comparable to that achieved after TURP. During the last 2 years some reports have confirmed that it is possible to treat urinary retention due to BPH with the Prostakath

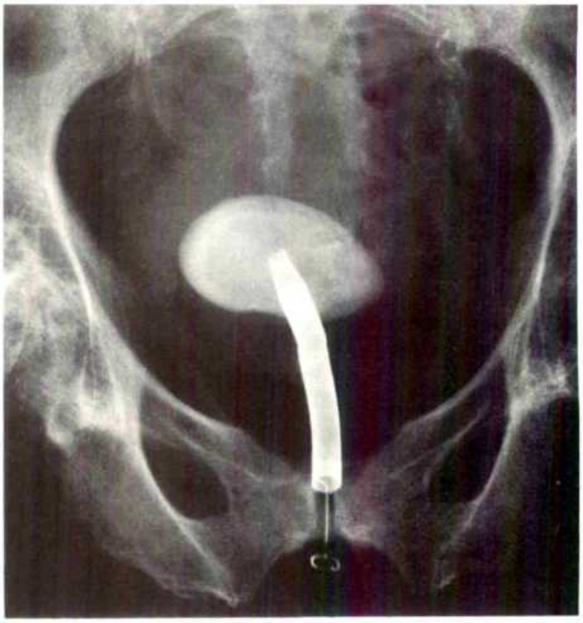

Fig. Plain X-ray of bladder region showing the Prostakath with stone formation.

stent and achieve an unobstructed voiding pattern (Nordling *et al.*, 1989; Harrison and De Souza, 1990; Nielsen *et al.*, 1990; Yachia *et al.*, 1990).

This is an attractive non-surgical alternative to permanent catheterisation, especially among patients in operative high risk groups. Since this self-retaining intra-urethral device seems to be increasingly popular, it is important to discuss the advantages and complications.

We used ultrasonic scanning to position the spiral as recommended by Nordling *et al.* (1989). This technique is not mandatory (Harrison and De Souza, 1990) because the Prostakath can be inserted under direct vision. Our patients experienced only minor local discomfort, but in 11 cases the stent had to be repositioned in order to achieve free voiding.

Our long-term success rate with the Prostakath was 55%, with a median follow-up period of 22 weeks. This is in accordance with the findings of Harrison and De Souza (1990). The primary complications which led to removal of the stent were urinary incontinence or urinary retention as described by Nordling *et al.* (1989), Harrison and De Souza (1990) and Yachia *et al.* (1990). Sandermann (1990) was the first to observe calcification on the Prostakath leading to removal of the stent. During a 12-month follow-up period, Nielsen *et al.* (1990) observed only a small amount of encrustation in 1 of 45 consecutive patients treated with the Prostakath, and this did not lead to infravesical obstruction or side effects.

It is an open question why severe stone formation occurred on the stent, since the gold-plated surface is believed to be inert to the urothelium and to urine. The surface of the devices that had been removed were examined by light microscopy for possible defects and it was concluded that no technical faults in the stent led to the stone formation. All 5 patients with calcification had chronic bacteriuria despite adequate antibiotic treatment and we suspect that long-standing infection is the main cause of encrustation (Cox *et al.*, 1989).

In patients with chronic bacteriuria we advocate regular plain X-ray of the bladder region to diagnose calcification of the stent. This late complication was identified an average of 44 weeks (range 21–82) after insertion of the Prostakath. In infected patients, who may develop calcification of the device, it may be advisable to change the stent at 6-monthly intervals. In surgical high risk patients treated with the Prostakath it is mandatory to avoid complications that might involve open surgery under general or regional anaesthesia.

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Calculation of Irrigant Absorption by Measurement of Breath Alcohol Level during Transurethral Resection of the Prostate

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Summary—If ethanol is added to the irrigant used in transurethral resection of the prostate, absorption of the fluid can be immediately detected by measuring the ethanol concentration in the expired breath. During 90 resections where the irrigant contained 1.5% glycine and 1% ethanol, the breath alocohol level was compared with the amount of irrigant absorbed as determined by volumetric measurement. The results showed that the expired-breath ethanol level depended not only on the volume of irrigant absorbed but also on the rate of ethanol diffusion in the total body water, which increased with the ethanol concentration. By applying a derived mathematical model the absorption could be estimated from the breath alcohol level at any time during surgery, with a median deviation of 19% from the measured value.

Ethanol monitoring is a simple and non-invasive method for detecting irrigant absorption during transurethral resection of the prostate (TURP). After the addition of a small amount of ethanol to the irrigating fluid the absorption is indicated by the ethanol concentration in the exhaled breath (EB-ethanol) (Hultén *et al.*, 1986). A rough estimate of the total absorption can be obtained from the highest EB-ethanol value recorded during TURP (Hultén and Hahn, 1989). The aim of this study was to derive an appropriate dynamic mathematical expression for the relationship between the volume of irrigant absorbed and the ethanol concentration in the expired breath.

Patients and Methods

TURP was performed in 90 patients. Their median age was 70 years (range 54–85), the resection time 43 min (15–95), the weight of tissue removed 28 g (6–70) and the blood loss 370 ml (59–2200).

Procedure

Consent for the study was obtained in all cases. Oxazepam 25–50 mg (Sobril, Kabi, Sweden) was given orally as premedication. Epidural analgesia was induced. A Storz 27 F resectoscope and the intermittent bladder filling technique were used in all of the operations. The irrigating fluid employed during resection was water containing 1.5% glycine and 1% ethanol (w/v) (Baxter, Sweden); after the operation it was 0.9% saline.

Measurements

Fluid balance. The irrigating fluid bags were weighed before and after use. To each collecting bucket approximately 1000 iu heparin were added to prevent clotting. For 50 patients the irrigant bag and the collecting bucket were changed every 10 min, and the fluid volumes and blood loss were carefully measured (Hahn, 1989). The volumetric fluid balance so obtained was corrected for the blood haemoglobin level (Hahn, 1987). In the remaining patients a volumetric fluid balance was recorded during 10-min periods only when the EB-ethanol test indicated absorption.

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Breath alcohol. The end-expiratory ethanol concentration was measured every 5 min during surgery with an Alcolmeter S-D2 (Lions Ltd, Barry, UK) (Fig. 1). The values so obtained represented the corresponding blood ethanol concentration, in steps of 0.05 mg/ml, from 0 to 9.95 mg/ml (1 mg/ml = 21.7 mmol/l). The Alcolmeter was calibrated before each procedure.

Results

Ethanol absorption was detected in 29 of the 90 patients. The relationship between the volume of irrigant absorbed (Abs) and the change in the ethanol concentration of the expired breath (ΔEB-ethanol) during any 10-min period of the operations may be expressed in terms of the general linear regression formula as the following equation:

$$\mathrm{Abs}_{10\,\mathrm{min}} = \mathrm{Factor} \times \Delta\mathrm{EB\text{-}ethanol} + \mathrm{Intercept} \qquad \text{(Eqn I)}$$

where the absorption is expressed in ml/10 min and the EB-ethanol in mg/ml. From the collected data it was apparent that a high EB-ethanol level at the beginning of a 10-min period attenuated the ethanol response to irrigant absorption (Fig. 2). Therefore, all of the 10-min periods where there was irrigant absorption ($n=83$) were divided into 5 groups according to whether the EB-ethanol level at the beginning of that period was 0 ($n=29$), 0.05–0.10 ($n=22$), 0.15–0.25 ($n=11$), 0.30–0.60 ($n=14$) or 0.65–1.10 mg/ml ($n=7$). Within each group there was a significant linear correlation between the change in the EB-ethanol level and the volume of irrigant absorbed. In order of increasing range for initial ethanol level, the following equations were obtained:

$$\mathrm{Abs}_{10\,\mathrm{min}} = 2108 \times \mathrm{EB\text{-}ethanol} + 67 \ \text{(Eqn II)} \quad r=0.91$$
$$\mathrm{Abs}_{10\,\mathrm{min}} = 2603 \times \mathrm{EB\text{-}ethanol} + 126 \ \text{(Eqn III)} \quad r=0.92$$
$$\mathrm{Abs}_{10\,\mathrm{min}} = 2816 \times \mathrm{EB\text{-}ethanol} + 223 \ \text{(Eqn IV)} \quad r=0.85$$
$$\mathrm{Abs}_{10\,\mathrm{min}} = 3488 \times \mathrm{EB\text{-}ethanol} + 351 \ \text{(Eqn V)} \quad r=0.92$$
$$\mathrm{Abs}_{10\,\mathrm{min}} = 5090 \times \mathrm{EB\text{-}ethanol} + 764 \ \text{(Eqn VI)} \quad r=0.84$$

These equations are summarised in Figures 3 and 4, from which it can be seen that there was a direct and significant relationship between the slopes and intercepts of these regression equations and the EB-ethanol level recorded at the beginning of a 10-min period of TURP (EB-ethanol$_i$). Thus, as indicated by Figures 3 and 4, the total absorption during the operation (Abs$_{\mathrm{tot}}$) can be expressed as the sum of the incremental absorptions during the 10-min periods according to the equation:

$$\mathrm{Abs}_{\mathrm{tot}} = \sum (2140 + 3430\ \mathrm{EB\text{-}ethanol}_i) \times \Delta\mathrm{EB\text{-}ethanol} + (44 + 806\ \mathrm{EB\text{-}ethanol}_i) \qquad \text{(Eqn VII)}$$

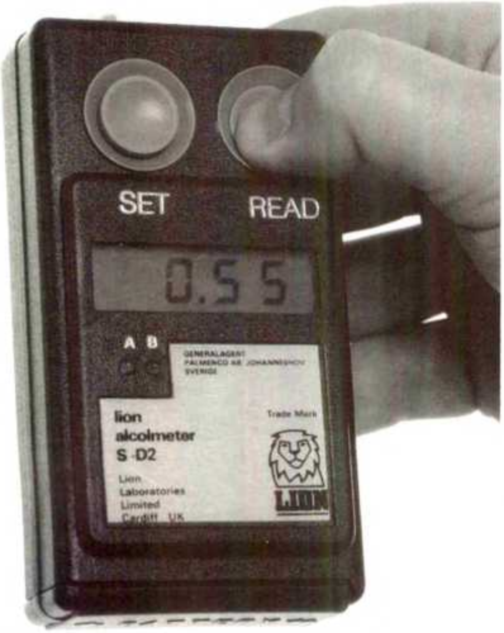
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Fig. 1 Pocket-size device for analysis of breath alcohol.

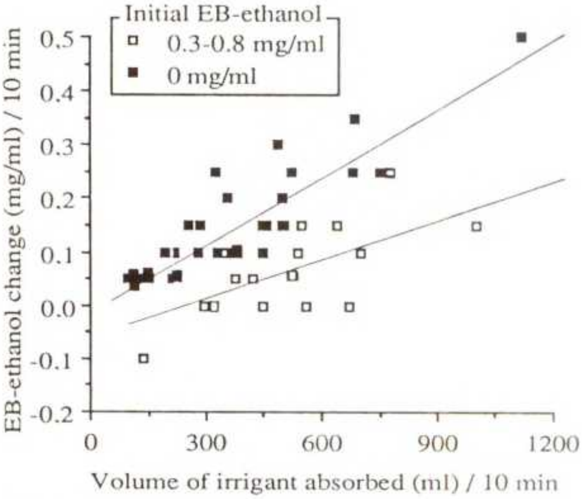

Fig. 2 The change in the expired-breath alcohol level (EB-ethanol) in response to irrigant absorption during 10-min periods of TURP starting with no detectable EB-ethanol and periods with an initial EB-ethanol level ranging from 0.3 to 0.8 mg/ml.

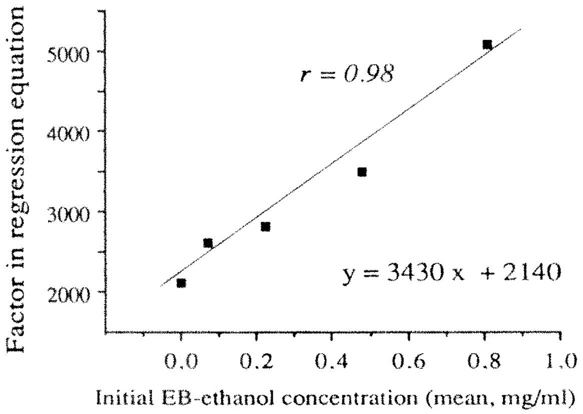

Fig. 3 Factors in the linear regression equations describing the relationship between the change in EB-ethanol and the volume of irrigant absorbed per one 10-min period of TURP *versus* the EB-ethanol at the beginning of the period.

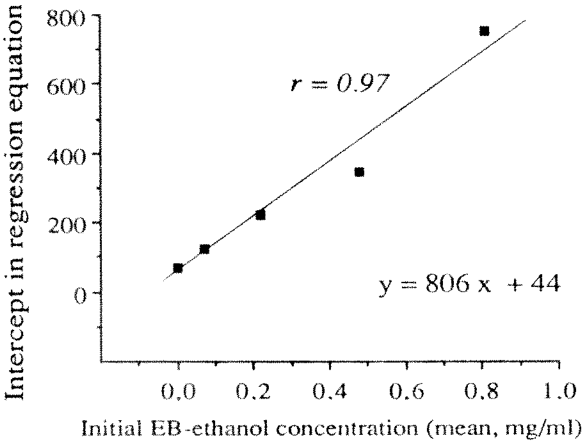

Fig. 4 Intercepts in the linear regression equations describing the relationship between the change in EB-ethanol and the volume of irrigant absorbed per one 10-min period of TURP *versus* the EB-ethanol at the beginning of the period (*i.e.* the volume of irrigant that must be absorbed in 10 min in order to keep the EB-ethanol constant).

Given the general appearance of the regression equation, the following one-step multiple regression equation was derived for 10-min periods where EB-ethanol$_i > 0$.

$$\text{Abs}_{\text{tot}} = \sum 7007\ \text{EB-ethanol}_i \times \Delta\text{EB-ethanol} + 632\ \text{EB-ethanol}_i + 202 \quad \text{(Eqn VIII)}$$

For a comparison, by linear regression analysis, of the measured cumulative volume of irrigant absorbed (median 665 ml, range 50–4330) and the absorption as calculated from Eqn II (EB-ethanol$_i = 0$) and Eqn VIII (EB-ethanol$_i > 0$), the correlation coefficient was 0.96 (Spearman Rho 0.94). The median error of an estimate according to these equations was 113 ml (17%). The median error of an estimate according to Eqn VII was 130 ml (19%).

Using multiple regression analysis, none of the correlations could be significantly strengthened by considering the patient's pre-operative body weight (76 kg, range 60–100) and serum creatinine concentration (mean 95 μmol/l, range 64–159).

Discussion

It is generally agreed that the "TURP syndrome" can be avoided by the early detection and treatment of irrigant absorption (Rao, 1987). This syndrome is observed in 1 to 7% of transurethral resections and may include hypertension, nausea, mental disorientation and circulatory shock (Rhymer *et al.*, 1985; Weis *et al.*, 1987; Hahn, 1989). However, as the bladder is impermeable to ethanol, data relevant to absorption can be obtained at any time during surgery simply by adding ethanol to the irrigant and testing the expired breath (Hultén *et al.*, 1986). This enables steps to be taken to prevent further absorption before the TURP syndrome can develop. Furthermore, the pattern of ethanol concentration in the expired breath makes it possible to distinguish between the essentially intra- and extra-vascular types of absorption (Hahn, 1989; Hultén and Hahn, 1989). The latter type of absorption may occur from open perforations in the prostatic capsule. However, in this hospital we have seen only a few patients with major extravascular irrigant absorption.

The aim of this study was to ascertain how to infer from data on the ethanol concentration in the expired breath the volume of irrigant absorbed. An attempt was made to derive a "best possible" equation that took into account the dynamics of EB-ethanol in connection with irrigant absorption and which was accurate enough for scientific purposes. The results were empirical. They showed that the EB-ethanol response to irrigant absorption depended not only on the amount of fluid absorbed during any period of an operation, but also on the ethanol level at the beginning of that period. As the initial EB-ethanol increased, the slope of the regression equation describing the relationship between the increments of irrigant absorption and EB-ethanol became less steep (Fig.3). Furthermore, absorption of a greater volume or irrigant was required just to keep the elevated EB-ethanol level constant (Fig. 4).

These results can be understood by considering the differences between a continuous and an interrupted intravenous infusion of ethanol. During continuous infusion, equilibrium soon develops between the ethanol added to the circulation, its oxidation and dispersal in the body fluids. In that case, the rate of ethanol supplementation is the main determinant of EB-ethanol. When the infusion is interrupted, the blood alcohol level falls rapidly because of continued distribution of the ethanol within the total body water. This process takes about 25 min to complete and if the ethanol is given for only 25 min, the final breath alcohol level will be about half of the peak value (Hahn, 1989; Hahn *et al.*, 1989). Hence, during this phase the magnitude of breath alcohol change is dependent upon the initial EB-ethanol value. Further lowering of expired-breath ethanol occurs much more slowly and by virtue of ethanol metabolism.

When using the intermittent irrigation technique during transurethral resection, irrigant can be absorbed only at the end of each filling of the bladder, *i.e.* when the pressure in the prostatic fossa exceeds that of the prostatic veins (Hultén *et al.*, 1984). Thus fluid absorption is likely to occur in a fashion similar to an infusion that is irregular intermittent and the dynamics of expired-breath alcohol during TURP will share features with both the continuous and the interrupted infusion of ethanol. Because a major part of the total amount of ethanol is usually absorbed within 25 min, there is a pronounced tendency for EB-ethanol to fall whenever absorption stops. If it continues, on the other hand, any further increase in an already high EB-ethanol level will represent a larger incremental volume of irrigant absorbed than when starting from a lower initial EB-ethanol level (Fig. 2).

The patient's pre-operative body weight and serum creatinine concentration appear to be of limited importance in this situation. Similarly, the effect of ethanol oxidation on the EB-ethanol level (about 0.15 mg/ml/h) is likely to be over-run by the impact of new absorption and ethanol dispersal.

The equation derived for calculating the volume of irrigant absorbed from EB-ethanol readings (Eqn VIII) can be programmed on a pocket calculator for quick reference. It is designed to give both the incremental absorption during any 10-min period of the resection, and the cumulative absorption during consecutive 10-min periods. The standard error of an estimate of cumulative absorption using this equation is only one-third of that obtained with a single EB-ethanol value, and one-half of that obtained with an EB-ethanol value corrected for absorption time (Hahn, 1989). One should note that the small remaining error is derived from both within-patient and between-patient sources.

In summary the volume of fluid absorbed and the dynamics of ethanol diffusion in the total body water are the main factors governing the EB-ethanol during absorption of ethanol-containing irrigating fluid. The results indicate that during transurethral resection the initial EB-ethanol concentration during any time increment can be used as an index of the dynamics of ethanol diffusion.

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Single-blind, Randomised, Parallel Group Study of the Bard Biocath Catheter and a Silicone Elastomer Coated Catheter

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Summary—A group of 69 community patients undergoing long-term urethral catheterisation for urinary incontinence took part in this study; 33 patients with a mean age of 70.03 years (±16.6) received the Dow Corning Silastic catheter (16 F 10-ml balloon) and 36 patients with a mean age of 75.61 years (±12.6) received the Bard Biocath catheter (16 F 10-ml balloon). Over a 16-week period catheters were monitored every 2 weeks and changed as necessary. The Bard Biocath catheter remained *in situ* for an average of 89.61 days (±35.31) and the Silastic catheter remained *in situ* for an average of 56.7 days (±38.8); this difference was statistically significant.

Used catheters were analysed for encrustation using scanning electron microscopy (SEM). The average time *in situ* for non-encrusted Biocath catheters was 83.7 days and 25.28 days for non-encrusted Silastic catheters.

It was found that 70% of patients who received Biocath catheters preferred them to their previous catheters whereas only 30% of patients in the Silastic group preferred the trial catheter. The incidence of bypassing was 28% in the Biocath group and 52.8% in the Silastic group.

Long-term indwelling catheterisation for the treatment of urinary incontinence is widespread within the community. Although a relatively cheap and convenient form of management, it may give rise to several complications, *e.g.* inflammation of the urethra, strictures, pressure ischaemia, infection, haematuria, and encrustation leading to eventual blockage of the catheter with mineral deposits.

The development of new base materials and coatings for catheters has gone some way to reducing these effects. At present the most commonly used catheter is silicone elastomer coated. This coating, which forms an elastic network of linear polymers with a high molecular weight on the surface of the catheter, has a reduced toxicity potential when compared with previous catheters. In addition, the silicone has a lower coefficient of friction and causes less irritation to the urothelium. Despite these advantages, however, this type of catheter is far from ideal and is still associated with a number of problems, the commonest being that the coating may not be chemically bonded to the substrate and may have a tendency to crack.

Bard Limited have developed the Bard Biocath Foley catheter, which consists of a latex substrate coated on the inner and outer surfaces with a special hydrophilic polymer that forms part of a class of compounds known as "hydrogels". These have extensive medical applications (Hoffman and Ratner, 1976) because of their inertness and high biocompatibility. Pre-clinical animal studies have indicated that the Bard Biocath catheter causes less irritation to the urothelium than an All-Silicone (100%) catheter (Davies, 1985). This has been confirmed in controlled clinical trials in hospital patients (Ferro and Smith, unpublished data). Controlled *in vitro* studies have also shown that the Bard Biocath catheter minimises the initial adhesion and build-up of encrustation over a long period and compares favourably with an All-Silicone

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Based on a Poster Demonstration at the 46th Annual Meeting of the British Association of Urological Surgeons in Scarborough, July 1990

(100%) Foley catheter (Cox *et al.*, 1988). Recent cell culture studies, in accordance with the recently published British Standard Method (British Standards Institution, 1990) have also given this catheter a zero cytotoxicity rating, indicating that no potentially cytotoxic substances are present which could leach from the catheter whilst *in situ*. Also, as the coating is chemically bonded to the substrate it will neither crack nor rub off. Laboratory testing has shown that immersion of the catheter in water at 100°F for 28 days does not affect the integrity of the coating.

Patients and Methods

The study group comprised 69 patients over the age of 18 years who were undergoing long-term urethral catheterisation. They were assessed as being mentally sound by a 10-point questionnaire. Patients with known sensitivity to hydrogel materials were excluded. Following recruitment, a clinical history was recorded. This included demographic details, previous catheterisation records, reason for catheterisation, information on the length of time the patients had been undergoing urethral catheterisation and the period of time their catheters normally remained *in situ*. The reason for change of their normal catheter was recorded, as were details of any washouts. Patients were then randomly allocated, using computer-generated random numbers, to receive either the Bard Biocath catheter (2-way 16 F 10-ml balloon) or the Dow Corning Silastic catheter (2-way 16 F 10-ml balloon) for 16 weeks.

Catheters were changed as necessary, each change being recorded together with details of the reason for change and assessment of comfort on removal and insertion of each catheter.

Patients were assessed at bi-weekly intervals. Problems associated with the catheter, medication changes, emergency visits, number of emergency washouts and comfort scores were recorded and a urine sample taken for analysis.

During the 16 weeks patients were requested to keep a daily diary card recording comfort, pain and leakage on a 3-point scale (1 = good; 2 = average; 3 = bad). At the end of the trial patients and nurses were asked to complete a questionnaire regarding the catheter and to score its performance with regard to insertion, removal, comfort, bypassing and drainage on a 5-point scale (1 = very good–5 = very bad). Catheter samples of urine were taken for microbiological analysis prior to entry into the study, at each 2-week assessment and on completion of the study.

All used catheters were placed in named sealable plastic bags and sent to the University of Manchester for analysis of any encrustation by SEM.

Any patient who required admission to hospital for more than 4 days was withdrawn from the study. Patients maintained their standard drainage system for the full study period.

Of the 69 patients in the study, 36 received the Bard Biocath catheter and 33 the Dow Corning Silastic catheter. Each patient was asked 10 questions to assess his or her mental state; a correct answer scored 1 point. A score below 5 excluded the patient from the study. The mean mental test scores were 9.02 for the Biocath subjects and 9.48 for the Silastic subjects.

Demographic data

The sex ratio of the patients in the Biocath group was 5 females (14%) to 31 males (86%) and in the Silastic group 7 females (21%) to 26 males (79%).

The mean ages of the patients were 75.61 ± 12.6 years (Biocath group) and 70.03 ± 16.6 years (Silastic group).

The mean weight and height of the 2 groups were 68.73 kg and 175.4 cm respectively (Biocath subjects) and 66.53 kg and 170.03 cm (Silastic subjects).

Details of previous catheterisation

Four patients (10%) in the Biocath group and 6 (18%) in the Silastic group had had no previous catheter.

Most of the patients who had been previously catheterised had used either the Silastic catheter (16 (55%) in the Biocath group and 10 (47.62%) in the Silastic group) or another make of silicone elastomer coated catheter (7 (24%) in the Biocath group and 5 (24%) in the Silastic group). Of the remaining patients in the Biocath group, 4 (14%) were using All-Silicone (100%) catheters and 1 (3%) was already using Biocath. In the Silastic group, 1 (5%) was using Biocath, 3 (14%) All-Silicone (100%), 1 (5%) plastic and 1 (5%) a Teflon (Dupont de Nemours) coated catheter.

The average size of the catheters was 16.5 F (Biocath group) and 16.0 (Silastic group).

The patients in the Biocath group had been using urethral catheters for an average of 37.53 months (± 49.94) and those in the Silastic group an average of 22.2 months (± 24.35); the 2 groups did not differ significantly.

Biocath patients changed their catheters on average every 77 days (± 66.9) and Silastic patients every 60 days (± 22.6); these values were not significantly different.

Table Reasons for Catheterisation

Diagnosis	*No. of patients (Biocath group)*	*No. of patients (Silastic group)*
Atonic bladder	1	0
Cancer (prostate/ bladder)	1	2
Cerebrovascular accident	3	1
Incontinence	2	4
Multiple sclerosis	3	5
Myocardial infarction	1	0
Paralysis	0	2
Parkinson's disease	0	1
Post-TURP incontinence	6	3
Prostatic enlargement	8	9
Retention	5	0
Spinal diseases	2	0

Reasons for catheterisation (Table)

The main reasons in both groups were prostatic enlargement, cerebrovascular accident, post-transurethral resection of prostate (TURP) incontinence, retention, incontinence and multiple sclerosis.

The majority of patients in both groups were ambulatory: 67% (Biocath) and 62% (Silastic); the other patients in the Biocath group were all wheelchair-bound. In the Silastic group 27% were confined to wheelchairs, 8% were bedfast and 4% chairfast.

Washout regimes

When the investigator/nurse was asked if washouts would be given intentionally during the study, 97% said no in the Biocath group and 92% in the Silastic group.

Pre-entry CSU

It was found that 72% of the Biocath patients had infected urine samples on entry to the trial compared with 86% in the Silastic group.

Results

Time in situ for each catheter during the study (Fig. 1)

The mean time that the catheters remained *in situ* prior to change or the end of the trial were 89.61 ± 35.31 days for the Biocath catheters and 56.7 ± 38.8 days for the Silastic catheters. Analysis using Student's unpaired *t* test showed the values to be significantly different ($P < 0.0014$).

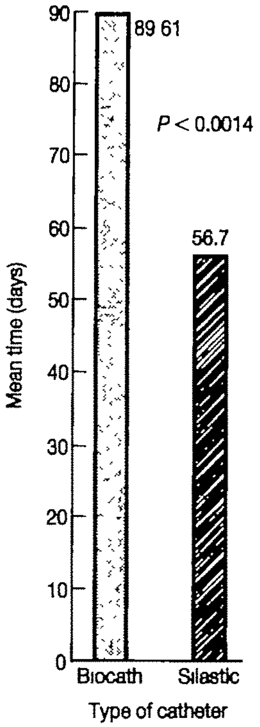

Fig. 1 Mean time *in situ* for Biocath and Silastic catheters.

Reason for change prior to completion of the study (Fig. 2)

Of 36 patients in the Biocath group only 9 required 1 or more catheter changes during the study period (25%). Of 33 patients using the Silastic catheter 20 required 1 or more catheter changes (60%) ($P < 0.006$ χ^2 with contingency correction). The total number of catheter changes for the 9 Biocath patients was 16. Of these 11 were for encrustation, 2 for bypassing, 1 for pain and discharge, 1 was pulled out and 1 was a routine change. The total number of catheter changes for the 20 Silastic patients was 38. Of these 9 were for encrustation, 21 for bypassing, 1 for pain and discomfort, 1 fell out and 6 were expelled.

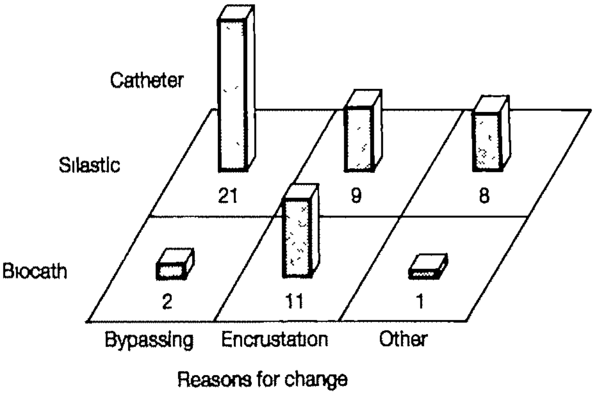

Fig. 2 Reasons for change of catheters.

Patient scores

On insertion and removal

No significant difference was found for the scores of comfort on insertion and removal of the catheter between the 2 groups.

Comfort of catheter in situ

These scores did not differ significantly between the groups.

Daily diary card scores

The mean daily scores for comfort, pain and leakage for the 2 groups were respectively 1.22 (Biocath), 1.30 (Silastic) (NS), 1.14 (Biocath), 1.24 (Silastic) (NS) and 1.12 (Biocath), 1.36 (Silastic) ($P<0.05$), showing significantly worse scores for leakage with the Silastic catheter (Mann Whitney U analysis).

End of trial scores

Patients scored comfort on insertion, removal and the catheter *in situ*, as well as the degree of bypassing, on a 1–5 scale where the higher the score the worse the rating. These scores did not differ significantly between the 2 groups.

Preferences

Sixteen patients (70%) in the Biocath group preferred Biocath to their previous catheter and 6 patients (30%) in the Silastic group preferred the trial catheter; this was significantly less ($P<0.029$) (χ^2 analysis).

Washouts

Of 48 reported washouts, 15 (31%) were in the Biocath group and 33 (68%) in the Silastic group ($P<0.001$) (χ^2 analysis).

Bypassing

Patients were asked to report any bypassing at each 2-week assessment visit; 226 and 179 responses were recorded in the Biocath and Silastic groups respectively. Of these, 50 bypassing episodes were recorded in the Biocath group (22%) compared with 62 in the Silastic group (35%) ($P<0.007$) (χ^2 analysis). Fewer responses were recorded in the Silastic group owing to higher patient withdrawal.

Encrustation (Fig. 3)

All catheters were removed and sent to the University of Manchester for encrustation analysis and SEM. The mean time *in situ* of the catheters with no encrustation was 83.7 days for the Biocath and 25.28 days for the Silastic catheters ($P<0.0003$) (Student's t test).

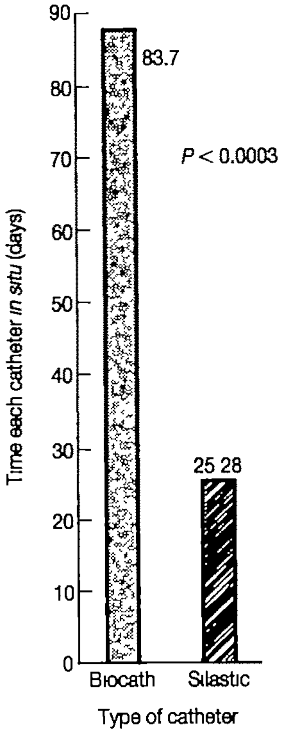

Fig. 3 Mean time *in situ* for non-encrusted catheters

Catheter specimens of urine

No difference was found at any point in the study between the amount of infected urine samples in each group. After 4 weeks 100% of patients had infected urine samples.

pH of urine (Fig. 4)

Urine pH was measured at 9 points throughout the trial. In both groups it rose significantly from the beginning of the trial to the end ($P<0.05$). Although the pH of the Biocath group remained lower at all points, the values did not differ significantly. The mean values over the study period were 6.3 (Biocath) and 6.6 (Silastic).

Withdrawals and adverse events

Of the 9 patients (25%) in the Biocath group who were withdrawn at some period in the trial, only 1 was due to a catheter-related problem. Of the remainder, 2 died, 5 were admitted to hospital for unrelated reasons and 1 was recatheterised with the wrong catheter.

Of the 12 patients (36%) in the Silastic group who were withdrawn, 7 were due to problems

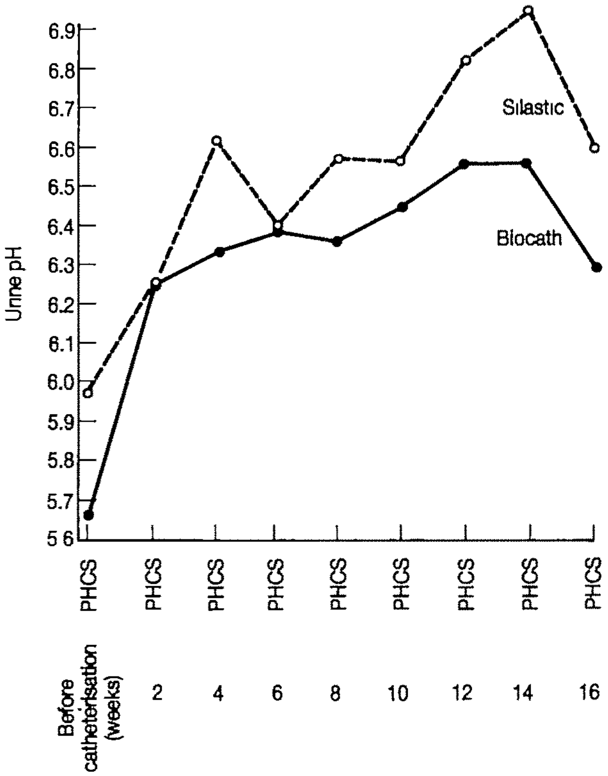

Fig. 4 Rise in urinary pH.

related to the catheter and were classified as adverse events, 5 were removed because of severe pain and bypassing caused by the catheter, 1 because the catheter would not drain, 1 because the catheter was repeatedly expelled, 4 died and 1 was wrongly recatheterised.

Discussion

The use of long-term Foley catheters for the management of micturition problems in community patients is known to lead to a variety of medical problems, namely infection leading to encrustation, blockage and leakage (Bruce *et al.*, 1974; Brocklehurst and Brocklehurst, 1978). These problems can also result in social problems for the patient. The catheters require extensive and time-consuming management for their maintenance, and frequent replacement can make catheterisation a costly form of treatment. This study has shown that the Bard Biocath hydrogel coated Foley catheter will remain in the patient an average of 2 months longer than the established Silastic Foley catheter. In addition, the occurrence of bypassing and leakage (as evidenced by the need to change the catheter and the patient's own diary card scores) was significantly less in patients using the Bard Biocath.

These results reinforce *in vitro* studies which have shown that the Bard Biocath catheter minimises initial adhesion and subsequent build-up of encrusting deposits (Cox *et al.*, 1988). This is due to the hydrogel coating, which has been shown to produce an ultra-smooth surface when compared with that of an All-Silicone (100%) catheter (Cox, 1987). Encrustation (the build-up of salts on the catheter as a result of the bacterial production of ureases which break down urine) is a major problem with catheters (Bruce *et al.*, 1974). It may cause trauma on removal of the catheter and lead to bypassing and blockage. This study has shown that the length of time for which the Bard Biocath remains unencrusted is significantly greater than that of the Silastic catheter; this is probably reflected in the lower occurrence of bypassing.

In addition to the above findings, this study has also shown that patients with the Bard Biocath catheter had fewer catheter-related adverse events. Over 50% of the patients withdrawn from the Silastic group experienced catheter-related adverse effects compared with only 11% of those withdrawn from the Biocath group. This difference is of clinical importance as it will influence the nursing time required for the patient and the incidence of hospital admission.

The patient's opinion of a catheter is important and it was found that of the patients who received the Biocath catheter, 69% preferred it to their previous catheter.

In conclusion, this study has shown that the Bard Biocath Foley catheter is preferable to the Silastic Foley catheter in the management of long-term catheterised patients in the community. It has the potential to reduce costs, nursing time, inconvenience to the patient and adverse catheter-related problems arising from long-term catheterisation.

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Gluteal Device for Penile Injection

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Summary—Locally acting vasodilator drugs have been used in the treatment of male impotence. Self injection, which may be most suitable in these circumstances, often presents difficulties. An implantable device was therefore used to make self injection possible for a wider selection of patients and 37 have now been treated successfully between January 1987 and September 1988.

Several vasodilator drugs have been used locally to induce semiphysiological erections in impotent men (Frydman *et al.*, 1984; Brindley, 1986). Papaverine hydrochloride is the most commonly used drug (Virag, 1982). Alpha blockers such as phenoxybenzamine and phentolamine mesylate have also been used to produce the same effect (Brindley, 1983). The combination of local vasodilators and alpha blockers in a ratio of 30:1 reduces the dose of each and still gives satisfactory results (Zorgniotti and Lefleur, 1985). However, apart from the limitations of the use of drugs (Halsted *et al.*, 1986; Larsen *et al.*, 1987), injection into the penile shaft also has disadvantages; it is painful, needs experience, and frightens some patients. For these reasons and because of its limited duration of action, the injection often needs to be carried out in a clinic. To overcome these difficulties and to make self injection feasible for suitable patients, a special device is implanted into the gluteal region.

Material and Methods

The implantable device (Fig. 1) is composed of 2 main parts: (1) an injection site consisting of a self-sealed rubber septum which accepts multiple injections without leakage. Behind this septum is a stainless steel plate which prevents the injecting needle from penetrating the device and a Dacron mesh for suture, all impregnated with silicone; (2) a connection catheter which starts from behind the septum and consists of a silicone cannula, with a narrow lumen and a 1-way valve to prevent regurgitation of blood into the cannula and with multiple dacron rings on the outside of the cannula. The rings are 2.5 cm apart and designed to hold sutures. Candidates for this operation are chosen according to the following criteria. All should be checked for a history of diabetes, the use of any drugs known to cause impotence, androgenic activity, thyroid function and prolactin levels. Complete general, urological, neurological and psychological examinations are carried out, together with a papaverine test and the penile-brachial index. The response to papaverine is assessed after delivering 60 mg of the drug diluted in 20 ml normal saline intracorporeally via a 23 gauge needle. In 3 to 5 min the penis starts to elongate and become turgid. The patient is assessed according to the degree of tumescence and categorised as having a poor, moderate or a firm erection (Gittes and McLaughlin, 1974; Kiely *et al.*, 1987). The test is repeated fortnightly 3 times and those who show moderate and firm erections in the 3 trials are candidates for the device. The penile-brachial index is derived using a 9.5 MHz Doppler stethoscope with a 3-cm cuff to measure the pressure in the dorsal arteries of the penis. The value is divided by the brachial artery pressure. Patients with values of 0.7 or more are potential candidates (Velcek *et al.*, 1980; Zorgniotti *et al.*, 1980; Lue *et al.*, 1985).

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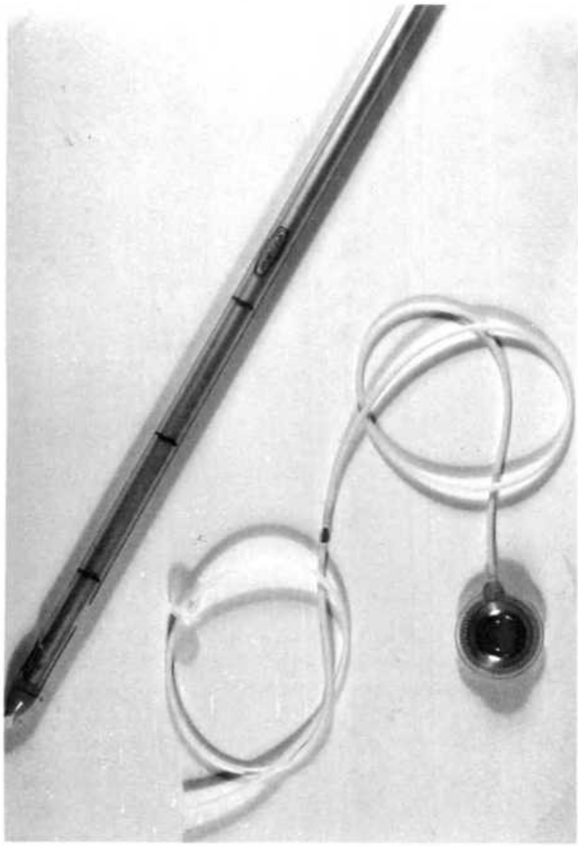

Fig. 1 The device.

Technique

Under general or local anaesthesia a semicircular incision is made in the upper outer quadrant of the gluteal region (Fig. 2). The gluteal fascia is opened and by blunt dissection a space is created to accommodate the injection site of the device, which is placed so as to avoid kinking of the catheter, and fixed in place by 3 to 4 non absorbable sutures. In obese patients, it can be inserted subcutaneously. An incision is made at the root of the penis and a metal tube is passed subcutaneously between the 2 incisions. The silicone cannula is milked through the metal tube until it appears from the other end. The metal tube is then withdrawn, leaving the cannula in place. The site of anastomosis is prepared by separating and cutting the fascia. Enough of the cannula is left to accommodate the erect penis and the remainder is removed. Between 2 stay sutures, a hole large enough to admit the cannula is made. The cannula is passed quickly to prevent bleeding from obscuring the hole. Only 1.25 cm of the cannula is introduced in order to avoid disrupting the cavernous tissue and the nearest ring is secured to the edge of the hole. Normal saline is injected through the septum to secure patency of the cannula before the wound is closed. During the first 3 post-operative weeks the patients are taught self injection with saline only. At a later stage the vasoactive drugs (papaverine hydrochloride and phentolamine mesylate in the ratio of 30:1) are injected under medical supervision. The prescribed dose was 7.5 mg papaverine HCl combined with 0.25 mg phentolamine mesylate or multiples thereof.

Results

A total of 37 patients have now been treated. Twenty patients use the device regularly and 13 said that although they could often achieve an erection without using the device, they preferred to retain it. One patient needed revision of the gluteal part and readjustment of the cannula, which was kinked. In 2 cases the cannula had to be replaced because of obstruction that could not be cleared. One patient did not respond to injection through the device but did respond to a direct injection. At exploration the tip of the cannula was found to have slipped and replacement restored function.

Eight patients married after the operation; 21 were already married and have resumed sexual activity. Two have had penile prostheses. In 6 cases no information was available. Ten patients still use the device and claim that they needed a 1.5 to 2-fold increase in the prescribed dose after a few months.

Discussion

Despite efforts in recent years to determine the aetiology of impotence, the number of patients in whom no cause can be found remains high and in them the cause is often described as psychological. Even when the aetiology is known, some patients with organic lesions have little hope of cure. Attempts to revascularise the penis in cases of extra-penile stenosis or occlusion are reported to restore potency, but long-term results have been poor. Ligation and stripping of the deep dorsal veins, and anastomosing the inferior epigastric artery to the deep dorsal vein to decrease the venous outflow in venogenic impotence, appear promising but few cases have been reported and long term results are not available. For patients with untreatable pathology, implantation of a penile prosthesis

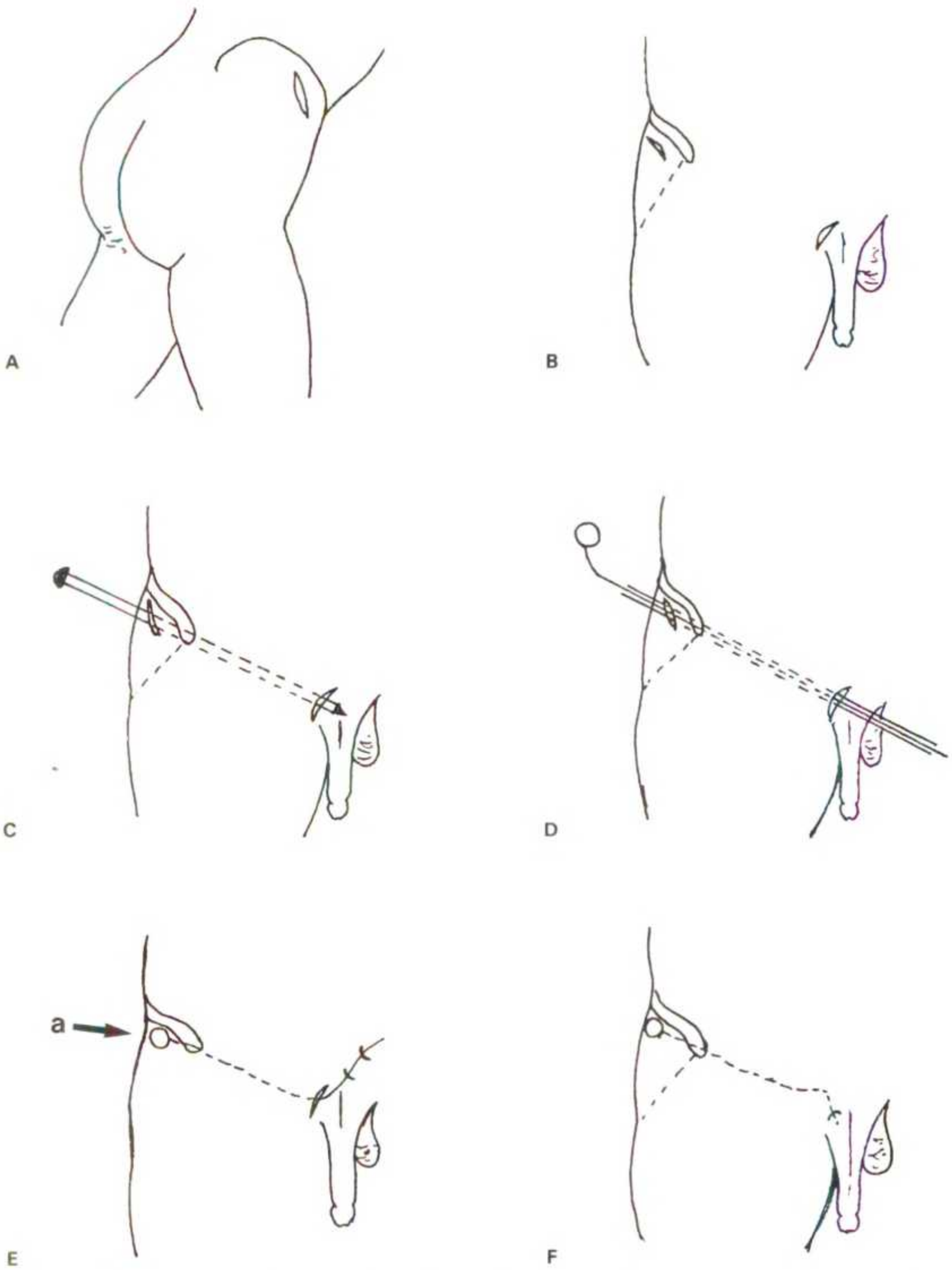

Fig. 2 (A) An incision is made in the upper outer quadrant of the right or left gluteal region. (B) Another incision is made at the root of the penis towards the side to be anastomosed. (C) A wide trocar and cannula are passed subcutaneously from the gluteal incision to the penile one. (D) The trocar is removed and the catheter is passed through the cannula which is then withdrawn. (E) The injection site (a) is fixed. An adequate length of the catheter is left to allow for erection and the rest is removed. (F) The catheter is introduced into the corpus and a Dacron disc is sutured around to secure it.

is an alternative, but is generally considered only after trying less invasive methods.

Patients for whom no specific treatment is available can be divided into 2 groups, depending on their response to intracavernosal vasoactive injection. For those who fail to respond, a penile prosthesis may be a satisfactory solution. For those who do respond, the induction of a semiphysiological erection by means of vasoactive drugs is an acceptable form of treatment.

The repeated delivery of vasoactive drugs intracorporeally has certain disadvantages. It may cause pain, haematoma, infection and eventually fibrosis. Because it is effective for only a short time, injections administered in a local clinic are of limited use and teaching the partner to administer the injection is not always feasible. The technique described is a simple method that allows the patient to inject himself in an easy and convenient manner and it does not destroy any of the cavernous tissues. The device is easily inserted and can be safely removed at the patient's request. It is unnecessary for the patient to inject himself on every occasion and the drugs can be kept in reserve. Should the drugs become ineffective, or should fibrosis develop, the patient will be better prepared psychologically to accept the implantation of a penile prosthesis.

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A Comparison of Aspiration, Antazoline Sclerotherapy and Surgery in the Treatment of Hydrocele

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Summary—Of 98 hydroceles (mean volume 125 ml) in a consecutive series of 92 patients, treated initially by aspiration, 14% (mean volume 70 ml) were cured.

The 76 recurring hydroceles (mean volume 146 ml) were then randomised to either antazoline sclerotherapy on an out-patient basis or surgery. Cure rates were 89 and 100%, respectively, at follow-up 6 months later. Operated patients were admitted for a mean duration of 2.5 days.

The results indicated that aspiration alone was inadequate, and sclerotherapy is advocated as the first choice of treatment for hydrocele.

Sclerotherapy seems to be an attractive alternative to surgery in the treatment of hydroceles. Antazoline (Antistin, Ciba-Geigy), primarily known as an antihistamine, possesses a sclerosing capacity; its curative effect on hydrocele at first seemed dubious (Lindskog, 1968), but the results of a more extensive study (von Rutte, 1978) were promising. The aim of this study was to compare the effects of aspiration alone, antazoline sclerotherapy, and surgery on hydrocele.

Patients and Methods

The study group comprised 92 adult patients referred consecutively to 3 departments. The median age was 64 years (range 19–65). Six patients had bilateral hydroceles. The sample thus consisted of 98 hydroceles but excluded previously treated ones. Also excluded were patients in whom we suspected an underlying testicular malignancy, or who were allergic to antazoline. The trial complied with the requirements of the Helsinki Declaration.

All hydroceles were emptied completely by aspiration through a plastic intravenous cannula (18 gauge, Vigo Venflon). All aspirates consisted of a clear, yellow fluid and contained no spermatozoa. The patients were supplied with elastic pants to be worn for 1 week after aspiration. Follow-up was scheduled at 1, 2, 3 and 6 months.

In the event of recurrence, patients were allocated to either sclerotherapy or operation. For the sclerotherapy procedure the hydrocele was first aspirated, then 2 ml of antazoline, 50 mg/ml, were injected. In hydroceles exceeding a volume of 50 ml, 4 ml of antazoline were injected. Neither local anaesthesia nor analgesics were given. Elastic pants were provided for 1 week's use. At recurrence, sclerotherapy was repeated up to a maximum of 3 times. If recurrence took place after the third injection, it was regarded as failure of treatment. Patients were observed for 6 months after the last sclerotherapy.

Surgery was performed on an in-patient basis and under general anaesthesia according to Winkelmann (1898) or Lord (1964). The choice of operative procedure was left to the surgeon. The patients were observed for 6 months post-operatively.

Results

During the study 98 hydroceles were aspirated. One patient was excluded because a testicular tumour was palpated after aspiration. Five patients did not appear for follow-up and were excluded; 92 hydro-

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celes were seen as scheduled. Thirteen did not recur but 79 recurred after a mean of 1.1 months after aspiration (range 1–6 months). This gives a cure rate of 14% by aspiration only (8–23%, 95% confidence interval). Three patients refused further treatment. A total of 76 hydroceles were randomised for further treatment. Of the 40 hydroceles treated with sclerotherapy, 11 were cured after a single injection. Four were excluded after the first sclerotherapy session. Of these 4, 3 were recurrences and the patients chose to undergo surgery; 1 could not be traced at follow-up after 6 months. Fourteen patients were treated twice and 13 cured; 1 requested surgery for his recurrence. Eleven hydroceles were treated three times; 7 were cured and 4 recurred. Thus 89% going through the entire sclerotherapy programme were cured (73–97%, 95% confidence interval). The results are listed in Table 1.

Table 1 Results of Treatment

Treatment	*No of hydroceles*	*Mean hydrocele volume (ml)*	*Cured (%)*
Aspiration only	22	70	13/92 (14)
Sclerotherapy	40	145	31/35 (89)
Surgery	36	149	16/16 (100)
Total	98	125	—

The volume of the hydroceles cured by aspiration alone (mean 70 ml) was significantly smaller than the volume of the whole group (mean 125 ml); $P=0.01$) (Mann–Whitney rank sum test).

The volume of hydroceles cured by a single sclerotherapy session (mean 85 ml, range 25–420) was not significantly different from that of those requiring 3 injections (mean 150 ml, range 70–230); $P=0.57$) (Mann–Whitney rank sum test).

In the group of hydroceles that were aspirated, only 1 patient developed infection; he responded to antibiotics and the hydrocele did not recur. In the sclerotherapy group 3 patients described episodes of minor pain during the first 2 weeks following the initial sclerotherapy. One patient complained of tenderness on palpation at follow-up after 6 months. None of the patients complained of pain during the sclerotherapy procedure. None of the antazoline-treated hydroceles developed infection or haematoma at the site of injection. No systemic side effects were observed after sclerotherapy and no admissions to hospital were required.

In the group of surgically treated hydroceles, 16 patients (44%) complied with the criteria of the follow-up at 6 months; 1 patients developed a haematoma post-operatively. No infections or recurrences were seen. The surgically treated patients were admitted for a mean duration of 2.5 days (range 1–7). All patients engaged in active employment had a minimum of 1 week's sick leave.

Table 2 Sclerotherapy for Hydrocele

Reference	*Sclerotic agent*	*Prospective Y/N*	*No of hydroceles*	*Mean volume (ml)*	*Follow-up (months)*	*Cure rate (%)*
Lindskog (1968)	Antazoline 2 ml	Y	23	—	6	19
von Rutte (1978)	Antazoline 2–6 ml	—	146	—	12–120	85
Bødker *et al.* (1985)	Tetracycline 10%	Y	10	180	6	90
Bullock and Thurston (1987)	Tetracycline 10%	Y	38	240	9	95
Levine and De Wolf (1988)	Tetracycline 10%	—	28	150	15	93
Lund (1988)	Aetoxysclerol 3%	Y	8	195	12	63
Thorup *et al* (1986)	Tisseel 4 ml	Y	21	75	3	38
Larsen *et al.* (1986)	Tisseel 1–2 ml	Y	35	200	2	0
Hellstrøm *et al.* (1986)	Ethanolamine oleate	Y	11	135	8	100

Discussion

Morbidity, recurrence rate and duration of admission in relation to surgery for hydroceles (Bødker *et al.*, 1987) all call for alternative forms of treatment. Aspiration was found to be simple to perform and acceptable to the patients, without the need for local anaesthesia. Lindskog (1968) in his sclerotherapy series reported infection in 1 of 21 patients and cured only 4/21 with antazoline. Several reasons could account for this poor result: a 2-ml dose of antazoline for all hydroceles regardless of volume was probably too small; no support was provided after aspiration and a 2-week observation period following sclerotherapy was too short, since the effects of chemical irritation can simulate recurrence for 6–8 weeks (Levine and De Wolf, 1988). The cure rate (85%) of von Rutte's (1978) series of 146 patients was comparable to that of this study. Table 2 lists a number of different agents used recently for sclerotherapy of hydroceles. Tisseel apparently has no therapeutic effect. Larsen *et al.* (1986) reported a recurrence rate exceeding that which one would have expected to find after aspiration alone. Among the listed drugs no definite priorities can be given. In Denmark, a 10% suspension of tetracycline is widely used. We have found no reports dealing with the problem of a possible teratogenic effect on the testis or the possibility of a mutagenic effect on the spermatozoa.

Lord (1964) found no haematomas or recurrences in a group of 22 surgically treated patients. Bødker *et al.* (1987) in a retrospective study found 11% with haematoma and 4% with infection in a group of 127 surgically treated hydroceles. We suggest that surgery be reserved for the following indications—(1) suspicion of malignancy in the testis and (2) patients still wishing to procreate—until prolonged follow-up studies have been carried out to exclude the possible mutagenic effect of sclerotherapy.

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Epididymectomy for Post-vasectomy Pain: Histological Review

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Summary—Fifteen epididymectomies were performed on 10 patients with post-vasectomy pain and 12 specimens were available for histopathological review. The findings were compared with those in 2 groups in which epididymectomy was performed for chronic epididymo-orchitis and epididymal cysts. The results showed that 50% of the post-vasectomy group were cured by simple epididymectomy. Pathological findings revealed features of long-standing obstruction and interstitial and perineural fibrosis which may have accounted for the pain. It is important to recognise this late complication of vasectomy and, if surgery is to be performed, to include all of the distal vas and previous vasectomy site in the excision.

Vasectomy is a common operation which has few complications and is almost always carried out for contraceptive purposes. Esho *et al.* (1973), in reviewing 400 consecutive vasectomies, reported an early complication rate of 12.85% and a late complication rate of 4.3%. Most of these complications were trivial and resolved either spontaneously or with simple treatment; 3% of the subjects developed a tender lump at the vasectomy site. Testicular or epididymal pain following vasectomy is less common and has been attributed to infection, testicular engorgement due to blockage of sperm transport, extravasation of sperm with sperm granuloma formation, and trapping of nerves in ligatures. The term "late post-vasectomy syndrome" has been coined for the unremitting pain due to long-standing obstruction following vasectomy (Selikowitz and Schned, 1985).

The majority of patients with testicular or epididymal pain following vasectomy settle with conservative management. However, the pain persists in a small number despite treatment with antibiotics and non-steroidal anti-inflammatory drugs. Many patients are satisfied by reassurance that it is nothing serious, but in those in whom the symptoms are severe, surgery will be required. Excision of sperm granulomas, epididymectomy and vasovasosotomy have all been recommended (Schmidt, 1979; Shapiro and Silber, 1979; Edwards and Errey, 1982; Selikowitz and Schned, 1985).

We describe the clinical results of epididymectomy in a group of patients with post-vasectomy pain operated upon over a 5-year period. The pathological findings are described and compared with those in patients who underwent the operation for pain due to chronic epididymo-orchitis or for epididymal cysts. Most of the patients with epididymal pain following vasectomy had been treated with broad-spectrum antibiotics and analgesics. Some had been cystoscoped to exclude a urinary tract abnormality as the cause.

Patients and Methods

Ten patients with post-vasectomy pain were studied (Group I). The symptoms and clinical findings were reviewed. Five underwent bilateral epididymectomy and 5 unilateral epididymectomy. Histological examination was not undertaken in 2 subjects, but 12 epididymectomy specimens were available for review from 8 patients. During this period, 14 other patients also underwent epididymectomy: 7 for pain due to chronic epididymo-orchitis despite antibiotic treatment (Group II) and 7 for epididymal cysts (Group III). Seven epididymides were

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reviewed from 6 patients in the epididymo-orchitis group together with 5 epididymides from 4 patients in the epididymal cyst group.

All patients in Group I had sterile urine cultures and failed to respond to broad spectrum antibiotic treatment. Epididymectomy was performed between 6 months and 20 years (mean 7 years 7 months) after vasectomy. At operation, the epididymis was carefully dissected free from the neurovascular bundle and the epididymis and distal part of the vas deferens were excised. The previous vasectomy site was excised in only 4 cases.

Paraffin wax embedded sections were retrieved from the archives of the Department of Histopathology and reviewed. Particular attention was paid to the presence and extent of ductal dilatation and interstitial fibrosis and to the presence of so-called "brown patches" of the epididymis (Mitchinson *et al.*, 1975; Ball and Mitchinson, 1984) and of spermatic granulomas (Glassy and Mostofi, 1956).

The patients were reviewed 3 months following surgery, when evidence of persistent pain and tenderness was sought. The clinical results were graded as good when there were no residual symptoms and as poor when pain and tenderness persisted or where further surgery was required.

Results

Half of the patients in Group I complained of bilateral testicular pain and the remainder of right-sided pain only (Table 1). The onset of pain varied from 1 month to 20 years (mean 6 years) following vasectomy and the mean duration of pain prior to epididymectomy was 18.4 months (range 6–56); 90% of the subjects complained of a constant dull ache in the scrotum and only 1 complained of constant severe pain, in this case associated with tenderness at the vasectomy site (case 4). Four had exacerbation of the pain during physical activity and 3 during sexual intercourse. All patients had a tender site and, apart from case 3, testicular and/or epididymal swelling.

Operative results

Only 5 of the 10 patients who underwent epididymectomy in the post-vasectomy group (Table 2) were considered to have had a good result. In these cases epididymectomy had been carried out between 6 months and 10 years after vasectomy. Two of these subjects had undergone bilateral epididymectomy and 3 unilateral epididymectomy. In 2, the site of vasectomy was excised with the epididymis. Of the 5 subjects with poor results, 1 (Group I, case 8) eventually underwent orchiectomy with symptomatic improvement. The remaining 4 have persistent pain despite antibiotic treatment and have been offered orchiectomy. There was no obvious association between the clinical characteristics and the outcome of epididymectomy (Tables 1 and 2).

Table 1 Clinical Features

	Patient no.									
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Side Bilateral		•	•	•	•				•	
Right	•					•	•	•		•
Left										
Duration (months)	6	6	21	30	56	12	24	12	12	5
Onset of pain following vasectomy (years)	0.08	0.5	1	0.08	0 33	4	8	12	15	20
Nature of pain										
Constant		•	•	•	•	•	•	•	•	•
During activity	•		•		•		•			
During intercourse	•		•						•	
Site of tenderness										
Testis		•			•			•		
Epididymis	•		•	•	•	•	•	•	•	•
Vasectomy site				•						
Testicular swelling		•			•	•	•			
Epididymal swelling	•			•		•	•	•	•	•

Table 2 Group I. Post-vasectomy

Case no.	*Age (years)*	*Time of surgery since vasectomy (years)*	*Side*	*Histology*	*Ductal dilatation*	*Interstitial fibrosis*	*"Brown patch"*	*Spermatic granuloma*	*Clinical result*	*Comment*
1	33	0.5	Rt	Yes	+	0	0	0	Good	
2*	53	1	Bil	Yes Rt	+	+	0	0	Good	
				Lt	+	+	0	+		
3	43	1.9	Bil	Yes Rt	+	+	+	++	Poor	Vasitis nodosa. Orchiectomy offered
				Lt	+	+	0	0		
4*	46	2.5	Bil	No	N/A	N/A	N/A	N/A	Poor	Orchiectomy offered
5	39	5	Bil	Yes Rt	+	+	+	0	Good	
				Lt	+	+	+	0		
6*	35	5.8	Rt	No	N/A	N/A	N/A	N/A	Good	Previous excision of sperm granuloma at vasectomy site
7	43	10	Rt	Yes	+	+	+	0	Good	
8	45	13	Rt	Yes	++	++	+	0	Poor	Subsequent orchiectomy
9	41	16	Bil	Yes Rt	++	++	+	+	Poor	Orchiectomy offered
				Lt	++	++	+	0		
10*	59	20	Rt	Yes	+	+	0	0	Poor	Orchiectomy offered

0 = None.
+ = Present
++ = Pronounced.
N/A = Not applicable

* Excision of vasectomy site

Six of 7 patients in the epididymo-orchitis group (Table 3) had good results. The 1 patient with a poor result required an orchiectomy and excision of residual appendages and is now symptom-free. Four of the 7 patients who underwent epididymectomy for epididymal cysts (Table 4) had epididymal pain before surgery and all 7 had no further trouble afterwards.

Histopathology observations

Pathological material was available for review from 18 of the 24 patients. In many respects the 3 groups showed similar appearances. Mild ductal dilatation and interstitial fibrosis were seen in almost all epididymides examined and affected the head (efferent ductules) and the body and tail (epididymal duct) to a similar degree (Figs 1 and 2). Two patients examined many years after vasectomy and 1 patient in each of the other groups showed pronounced dilatation and fibrosis. "Brown patches" of the efferent ductules were present in 10 of the 24 epididymides examined. The appearances resembled those already described (Fig. 3) (Mitchinson *et al.*, 1975; Ball and Mitchinson, 1984) and, although relatively more pronounced in the post-vasectomy subjects, there was no obvious association with any particular group of patients. On the other hand, spermatic granulomas were found in only a minority of cases. They were present in 3 patients in Group I (Fig. 4) and 1 in Group II. In all of these cases the spermatic granuloma was related to the epididymal duct and in 1 case (Group I, case 3) there was an additional large spermatic granuloma at the site of vasectomy. It was associated with a suture granuloma and changes compatible with those of vasitis nodosa (Civantos *et al.*, 1972). In 1 other subject (Group I case 6) there had been previous excision of a spermatic granuloma at the site of vasectomy.

Many subjects, from all groups, showed moderate to pronounced thickening of the smooth muscle coat of the epididymal duct. Where interstitial fibrosis was pronounced, particularly in the tail of the epididymis or if related to the vas deferens, it often appeared closely to envelop nerves and, in some cases, caused obvious distortion and angulation (Fig. 5).

Discussion

Epididymectomy for post-vasectomy pain appears to have only a 50% chance of producing a good clinical result. On the other hand, when carried out for pain associated with chronic epididymo-orchitis or epididymal cysts, it is almost always completely successful. There was very little difference among the 3 groups in terms of the presence of dilated ducts and of interstitial fibrosis. However, in 2 of the long-standing cases in the post-vasectomy group these changes were particularly pronounced.

The role of spermatic granulomas in the aetiology of post-vasectomy pain is controversial. We found them to be more common in the post-vasectomy group: 3 of the 12 specimens had 1 or more and another man had had 1 excised previously from the vasectomy site. The true incidence of spermatic granuloma in these cases was probably higher, as they usually occur at the vasectomy site (Schmidt and Morris, 1973) and this was not often included in the specimen. The incidence of spermatic granuloma following vasectomy has been reported as 15 to 97% (Schmidt and Morris, 1973; Silber, 1977; Shapiro and Silber, 1979; Taxy *et al.*, 1981). In Shapiro and Silber's prospective study of 433 patients, of whom 97% were reported to have developed spermatic granulomas only 1 patient continued to complain of testicular pain and discomfort after 1 month. Schmidt (1979), on the other hand, found 54% of his patients were symptomatic with diagnosed spermatic granulomas following vasectomy and of these, 76% required surgery for relief of symptoms. Glassy and Mostofi (1956) reviewed 61 spermatic granulomas, 2 of which occurred after vasectomy, and found that 69% of their patients complained of pain and swelling.

We believe that late onset or prolonged post-vasectomy pain is due to at least 2 processes:

(i) Obstruction and dilatation of the efferent and epididymal ducts with interstitial fibrosis, as also described by Selikowitz and Schned (1985). Of 220 epididymides examined at vasovasostomy, 68% were turgid and distended, affecting mainly the caput epididymidis (Pardanani *et al.*, 1976). Such epididymal swelling, which was particularly pronounced in some cases many years after vasectomy, might have a variety of potentially painful secondary effects, including pressure on local nerves and vascular stasis and congestion.

(ii) Perineural inflammation and fibrosis following rupture of ducts and extravasation of spermatozoa. This occurs especially in the tail of the epididymis and around the vas after vasectomy. In several of our patients, nerves in these areas were densely encased in fibrous tissue and many showed severe distortion and angulation. In the subject with vasitis nodosa (Group I, case 3) there was also lymphocytic infiltration around nerves, implying

Table 3 Group II. Epididymo-orchitis

Case no.	*Age (years)*	*Duration of symptoms (years)*	*Side*	*Histology*	*Ductal dilatation*	*Interstitial fibrosis*	*"Brown patch"*	*Spermatic granuloma*	*Clinical result*	*Comment*
1	45	0.2	Rt	Yes	++	++	N/A	+	Good	Chronic suppurative epididymitis and vasitis
2	48	0.25	Rt	No	N/A	N/A	N/A	N/A	Good	
3	67	0.9	Bil	Yes Rt	+	0	0	0	Good	
				Lt	+	0	0	0		
4	36	1.1	Rt	Yes	+	+	0	0	Poor	Subsequent orchiectomy and excision of residual appendages
5	51	2	Rt	Yes	+	+	0	0	Good	
6	50	2.9	Rt	Yes	+	+	+	0	Good	Diverticula of vas
7	44	3	Rt	Yes	+	+	0	0	Good	

0 = None.
+ = Present.
++ = Pronounced.
N/A = Not applicable.

Table 4 Group III. Epididymal cysts

Case no.	*Age (years)*	*Symptoms*	*Side*	*Histology*	*Ductal dilatation*	*Interstitial fibrosis*	*"Brown patch"*	*Spermatic granuloma*	*Clinical result*
1	42	Swelling	Lt	Yes	+	+	0	0	Good
2	80	Swelling	Rt	No	N/A	N/A	N/A	N/A	Good
3	67	Pain and swelling	Lt	No	N/A	N/A	N/A	N/A	Good
4	48	Swelling	Lt	No	N/A	N/A	N/A	N/A	Good
5	66	Pain and swelling	Bil	Yes Rt	+	+	0	0	Good
				Lt	+	+	0	0	
6	44	Pain and swelling	Rt	Yes	+	+	+	0	Good
7	55	Pain and swelling	Lt	Yes	++	++	++	0	Good

0 = None
+ = Present.
++ = Pronounced.
N/A = Not applicable.

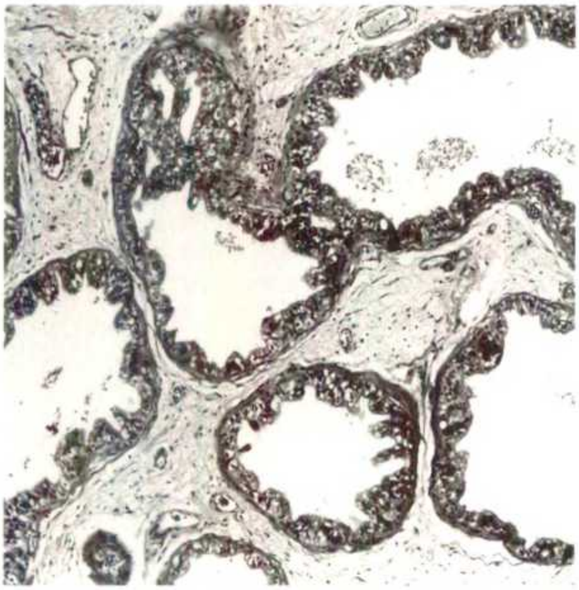

Fig. 1 Head of left epididymis from a 43-year-old man removed 1.9 years after vasectomy. There is dilatation of an efferent ductule with mild interstitial fibrosis. (H and E × 70).

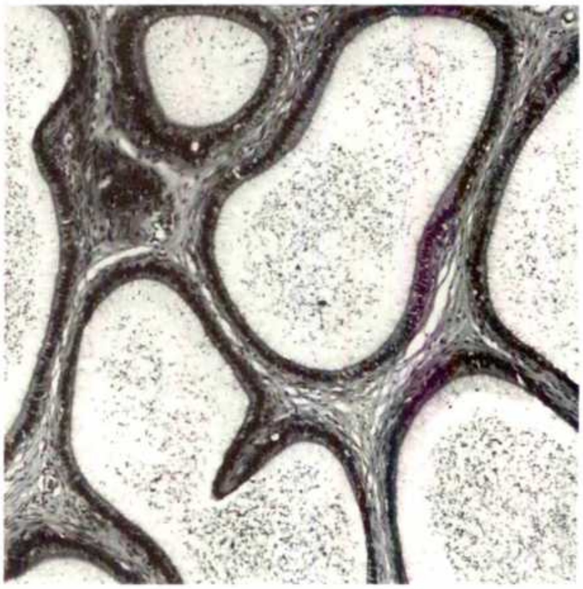

Fig. 2 Right epididymal duct removed from a 45-year-old man 13 years after vasectomy. There is pronounced ductal dilatation and interstitial fibrosis. The lumen contains degenerating spermatozoa. (H and E × 72).

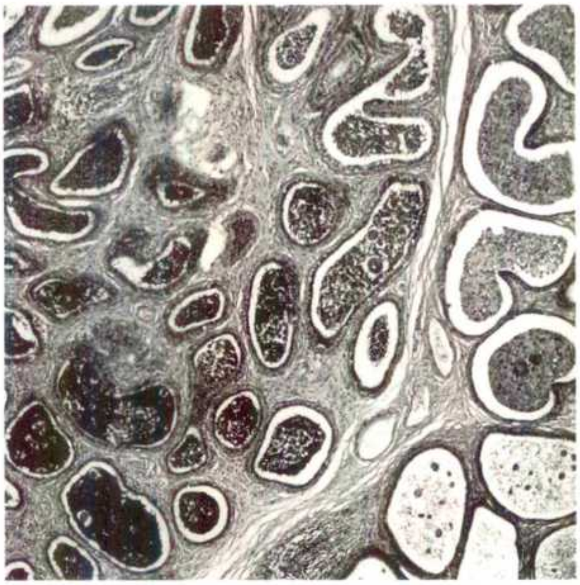

Fig. 3 "Brown patch" of the epididymis in a 45-year-old man 13 years after vasectomy. The efferent ductules are dilated and contain inspissated spermatozoa, spermatophages and cellular debris. There is interstitial fibrosis associated with focal accumulation of inflammatory cells, including pigmented macrophages. (H and E × 36).

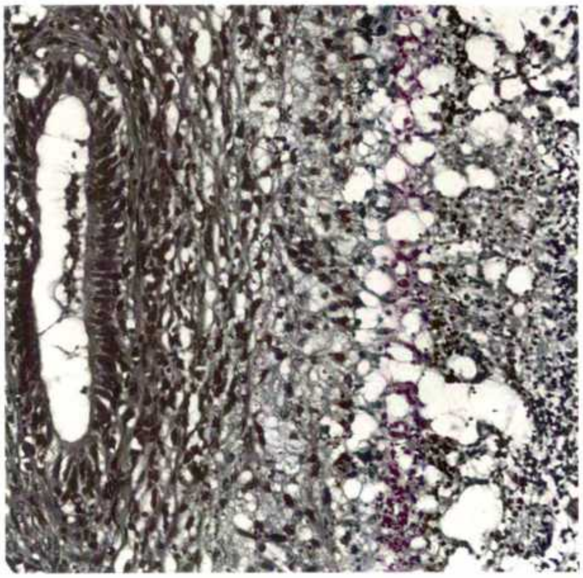

Fig. 4 Spermatic granuloma occurring in the body of the right epididymis of a 41-year-old man 16 years after vasectomy. Masses of extravasated spermatozoa (right) are bounded by a palisade of epithelioid cells and other mononuclear inflammatory cells (centre). Part of the epididymal duct is seen on the left. (H and E × 180).

an ongoing chronic inflammatory process affecting these structures. Nerves may also be invaded by epithelium-lined spaces in this condition (Taxy *et al.*, 1981).

The comparatively poor results of epididymectomy after vasectomy in Group I may be related to the persistence of perineural fibrosis, since the site of vasectomy was not usually excised. This is

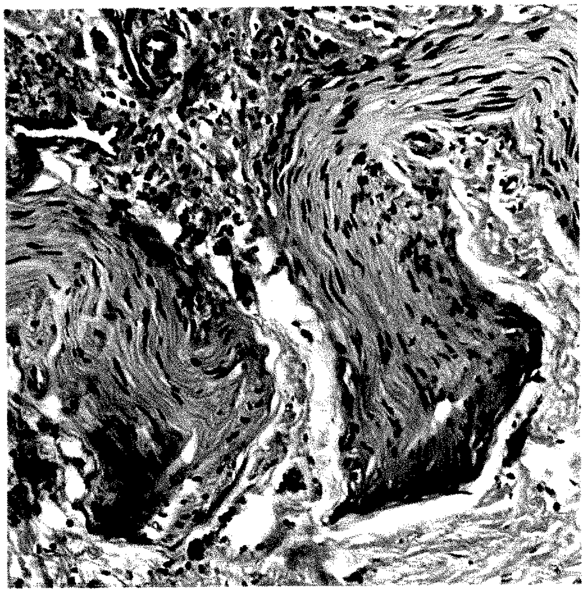

Fig. 5 Severely angulated and distorted myelinated nerves surrounded by dense fibrous tissue. In this example, removed from a 43-year-old man 1.9 years after vasectomy, there is also a dense lymphocytic infiltrate associated with the presence of vasitis nodosa and spermatic granulomatosis. (H and E × 180).

probably why Selikowitz and Schned (1985) achieved better results, for they dissected and excised the vas deferens up to and including the previous vasectomy site. However, in 2 of our 4 patients in whom the vasectomy site was excised with the epididymis, pain persisted. Much better results were obtained from simple epididymectomy for chronic epididymo-orchitis pain. In these subjects, distortion of nerves by fibrosis was not obvious. In the patient who had a poor result, subsequent orchiectomy showed pronounced perineural fibrosis.

Persistent post-vasectomy pain is uncommon and the incidence is undoubtedly low. However, vasectomy is a very common operation (4195 vasectomies were performed in 19 vasectomy centres of the Marie Stopes Clinic in 1989; personal communication), so that a significant number of cases of persistent post-vasectomy pain will be seen in a urological practice over a period of time. It is important to appreciate the non-infective origin of this pain, to prevent lengthy treatment with antibiotics, with little improvement, for a mistaken diagnosis of "chronic epididymo-orchitis".

The pathogenesis of this condition is possibly due to a combination of perineural fibrosis and long-standing obstruction, so that simple epididymectomy, if it is performed for this condition, will not be sufficient. We suggest that epididymectomy should be combined with excision of the whole of the distal vas up to the previous vasectomy site (including any scar tissue to be found there) if simple measures do not relieve the pain. This procedure should not be followed by the vigorous inflammation and fibrosis which may occur after vasectomy as spermatozoa would not be available locally to excite a granulomatous inflammatory process with subsequent severe fibrosis. However, even this procedure may not be successful and the patient may eventually require an orchiectomy.

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Fifteen-year Experience of Carcinoma of the Scrotum

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Summary—Between January 1975 and December 1989, 13 men were treated for carcinoma of the scrotum; 11 lesions were squamous cell and 2 basal cell carcinomas. Eleven patients initially underwent local wide excision and 1 local excision with inguinal node dissection. Two patients died of recurrent disease and 4 from unrelated causes, giving a corrected 5-year survival rate of 62.5%.

Although scrotal neoplasia has become synonymous with Pott (1775) and chimney sweeping, it had been described earlier by Bassius (1731) and Treyling (1740) (Lowe, 1983). In addition, this disease was prevalent among the nomadic tribesmen of Persia and Turkistan, who carried charcoal-filled pots under their robes for warmth.

Since the nineteenth century, scrotal carcinoma in the United Kingdom has more commonly been associated with other occupations, especially mule spinning in the cotton industry (Southam and Wilson, 1922). Volkman (1874) described this disease in tar workers and Bell (1876) in paraffin and shale oil workers (Fay, 1978). In the latter half of the twentieth century other occupations with significant worker exposure to oil have also been linked with this disease: machine operators in the engineering industry (Cruikshank and Squire, 1950), petroleum wax pressmen (Lione and Denholm, 1959), the screw-making industry (Tourenc, 1964) and automatic lathe workers (Avellan *et al.*, 1967). However, the decline of the cotton industry, better worker protection and hygeine have contributed to the falling incidence of this disease.

The experience with carcinoma of the scrotum in the Preston and South Ribble health areas from 1975 to 1989 is presented.

Patients and Methods

Between January 1975 and December 1989, 13 patients with scrotal carcinoma presented to the Royal Preston Hospital or Chorley District Hospital. In all cases the clinical diagnosis was confirmed histologically. Squamous cell carcinoma (SCC) accounted for 11 cases and basal cell carcinoma (BCC) for 2. The tumours were staged according to the classification proposed by Ray and Whitmore (1977) (Table).

The mean age at presentation was 78.5 years (range 70–85; median 77) (Fig. 1). All patients were of Caucasian origin. Eight had worked in the cotton industry as mule spinners, 2 as post office employees, and in 1 instance each as asphalter, engineer/turner and painter.

Results

Clinical presentation. Twelve of the 13 men presented with a slowly enlarging, painless, ulcerating lesion of the scrotum. In 1 patient advanced scrotal disease was noted as an incidental finding following admission for cerebrovascular accident (CVA) and bronchopneumonia.

At presentation, inguinal lymphadenopathy was present in 2 men. A further patient progressed to develop nodal involvement with subsequent death from metastatic disease (Table).

The median duration of symptoms prior to presentation was 6 months (range 3 weeks–5 years; interquartile range 6–24 months); 9/13 men presented within a year of noticing the scrotal lesion (Fig. 2).

Additional neoplastic disease. Three patients had an additional neoplastic diagnosis. Two men (1 with SCC and 1 with BCC of the scrotum) had

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Table Details of 13 Patients with Carcinoma of the Scrotum

Patient	*Histology*	*Stage*	*Occupation*	*Cause of death*
1	Well diff. SCC	A_1	Mule spinner	
2	Well diff. SCC	A_1	Mule spinner	Metastatic SCC
3	Well diff SCC	A_1	Mule spinner	
4	Well diff SCC	A_1	Mule spinner	CVA
5	Well diff. SCC	A_1	Asphalter	
6	Moderately diff. SCC	A_1	Mule spinner	
7	Poorly diff SCC	B	Painter	Metastatic SCC*
8	Well diff SCC	C	P O clerk	CVA/pneumonia*
9	Ulcerated BCC	A_1	Postmaster	
10	Ulcerated BCC	A_1	Engineer/turner	
11	Well diff SCC	A_1	Mule spinner	Carcinoma of oesophagus
12	Well diff. SCC	A_1	Mule spinner	CVA
13	Well diff. SCC	A_1	Mule spinner	

* Inguinal lymph node involvement at presentation.
BCC = basal cell carcinoma, CVA = cerebrovascular accident; diff. = differentiated, SCC = squamous cell carcinoma.

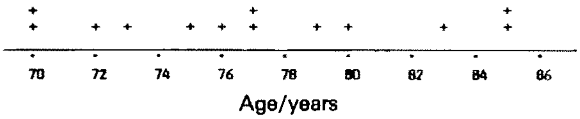

Fig. 1 Age at presentation.

multiple BCCs excised previously from the arms and face. A further patient with scrotal SCC died of SCC of the oesophagus.

Treatment: Stage A_1. The 11 men who presented with disease limited to the scrotum (including the 2 with BCC) were all treated by local excision of the scrotal lesion with a 1-cm clearance margin. Only 1 progressed to develop inguinal node metastases, 10 months after primary excision. Further treatment was not possible because of the patient's poor general condition, death being due to metastatic disease.

Three patients died from unrelated causes with no evidence of residual scrotal carcinoma. Two suffered fatal cerebrovascular accidents 5 and 10 years after diagnosis. One died of oesophageal carcinoma 15 months after treatment. Seven men are therefore alive and disease-free 9 to 80 months after local excision.

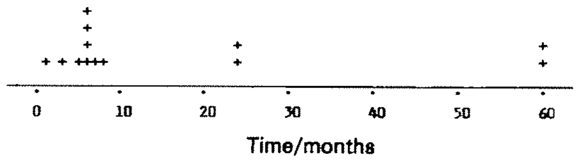

Fig. 2 Duration of symptoms prior to presentation.

Stage B. One patient presented with unilateral inguinal node enlargement. Local excision of the scrotal lesion was performed with nodal biopsy. Upon histological confirmation of node metastases, unilateral groin dissection was carried out. The patient died 18 months later from recurrent metastatic disease.

Stage C. One man presented with advanced local disease and regional metastases as an incidental finding during his final illness (see above). Five years earlier his family doctor had noticed a scrotal ulcer but treatment was refused by the patient.

Survival. Two patients died of SCC of the scrotum and 4 others died of causes unrelated to their scrotal tumour. Thus the corrected 5-year survival rate in this series is 62.5% (Fig. 3), with a median survival rate in excess of 60 months.

Discussion

Carcinoma of the scrotum is a relatively rare and declining disorder, with an estimated annual incidence of 0.1 to 0.3 per 100,000 (Clemmeson, 1965; Lowe, 1983). The highest reported incidence of scrotal cancer in this country has been in the heavily industrialised areas of Lancashire and Yorkshire, where the cotton and engineering industries have until recently been dominant. The decline in this disease not only reflects the decline of these industries and thus exposure to carcinogens, but also better hygeine and shelter from exposure. The majority of scrotal lesions are squamous. Although BCC is the most common of skin neoplasm, the scrotum is an unusual site, with a reported incidence

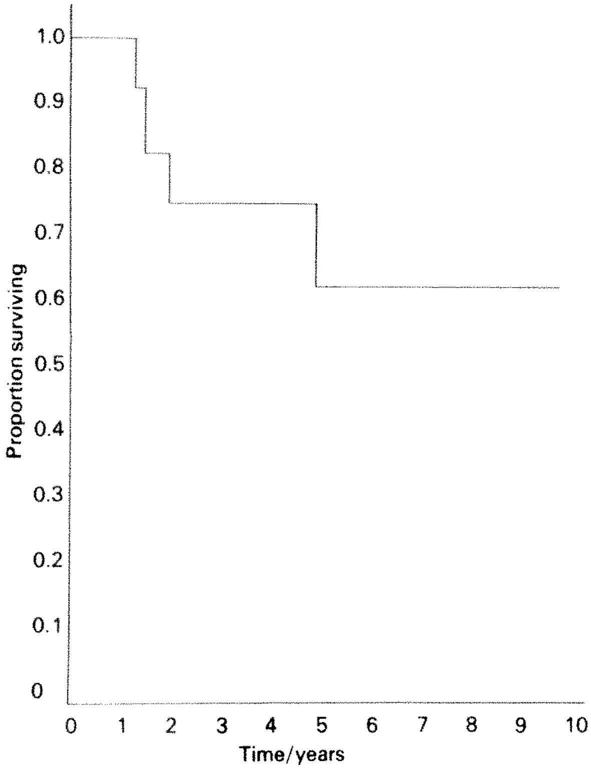

Fig. 3 Kaplan–Meier survival curve for scrotal carcinoma (13 patients).

of only 5 to 7% of all scrotal carcinomas (Kickham and Dufresne, 1967; Ray and Whitmore, 1977). The incidence in this series is higher at 15%.

Typically this order presents in the sixth decade of life (Lowe, 1983), but in this series the age at presentation was almost 20 years higher, with most patients being in their eighth decade. This may be because these men, although from a generation where industrial exposure to carcinogens was heavy, may have received less exposure themselves, or the latency period from contact to carcinogenesis was longer than normal.

In common with other reports (Kennaway, 1924; Henry, 1937; Lee and McCann, 1967; Lee, 1976), this study confirms the strong relationship between SCC of the scrotum and industrial exposure to machine oils and tar. The aetiology of scrotal BCC, however, is unclear and is probably multifactorial. Exposure to ultraviolet rays, ionising radiation, industrial oils and other chemicals may be implicated in this disease. One of our patients had BCCs removed from the face before and after presenting with a scrotal lesion, suggesting that a generalised epithelial instability may play a role in this particular skin neoplasm.

It has been suggested that SCC of the scrotum may be associated with other malignancies (Dean, 1948), especially skin, digestive and respiratory tract tumours (Holmes *et al.*, 1970; Ray and Whitmore, 1977; Waterhouse, 1977), but only 2 of our patients developed an associated malignancy, *i.e.* SCC of the oesophagus and multiple BCCs on the arms. The non-skin tumours in these patients may only be coincidental or may occur as part of a generalised tendency to malignancy, possibly due to an immunological deficiency or exposure to carcinogens which are active in different organs.

Metastases from squamous lesions are not uncommon; 3/11 men in this series developed inguinal node lymphadenopathy. Morley (1911) described the lymphatic spread of scrotal carcinoma, demonstrating that there was communication between the superficial lymphatics on both sides of the scrotum. Subsequent treatment was based on these findings, wide local excision with bilateral inguinal node dissection being recommended (Southam and Wilson, 1922; Graves and Flo, 1940). Dean (1948) and McDonald (1982), however, recommended lymphadenectomy only for biopsy-proven disease, it having been shown that node dissection is unnecessary in 75% of patients. Current surgical practice therefore consists of wide local excision. Sentinel node biopsy (Lowe, 1983) is a reliable test of whether lymphadenectomy is indicated. The results of wide local excision in this series support this mode of treatment.

Radiotherapy is generally held to be ineffective as primary therapy (Graves and Flo, 1940; Ray and Whitmore, 1977) and is usually reserved for palliation. Chemotherapy may be useful in advanced disease, especially with BCC (Stanley *et al.*, 1983), although toxicity is a major problem.

The prognosis of scrotal BCC is much better than that of SCC, with wide excision usually being curative providing the resection margins are free of tumour. Although rare, this tumour does have the potential to metastasise (Staley *et al.*, 1983), but long-term survival can be expected.

For SCC of the scrotum, survival is poor with sometimes a rapid death. In this series 24% were dead within 2 years. Similar figures have been reported by Cruikshank and Squire (1950). The corrected 5-year survival of 62.5% is better than that of most other reports. Kickham and Dufresne (1967) revealed that 78% of their patients were dead within 5 years. Dean (1948) reported a 5-year survival rate of 30%, and Ray and Whitmore (1977)

52%. Lione and Denholm (1959) had the best reported survival rate of 70% at 5 years, although many patients required multiple local excisions.

Survival correlates with disease stage (Ray and Whitmore, 1977) and this is reflected in this study, where only 1 patient with a stage A lesion died of scrotal carcinoma, whilst the man with a stage B tumour succumbed to the disease.

Although a relatively rare disorder, scrotal carcinoma, especially in squamous form, may be an aggressive disease. Good results can be expected only at an early stage of the disease, when wide local excision is the treatment of choice, with sentinel node biopsy if there is any doubt about inguinal node status.

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Thirty-year Review of Intrascrotal Rhabdomyosarcoma

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Summary—Between 1957 and 1987, 6 cases of intrascrotal rhabdomyosarcoma were found in the pathology records for Northern Ireland. Four of these tumours arose from paratesticular tissue and 2 were confined to the testis. Only 1 patient has died of his disease. Two were lost to follow-up after 21 years and are presumed cured. The remaining 3 remain alive and disease-free between 2 and 3½ years after presentation.

Case Reports

Case 1. A 78-year-old man presented in October 1986 with a 5-year history of increasing swelling of his scrotum. Examination showed a massively enlarged scrotum stretching almost to his knees. The swelling on the right side was due to an easily reducible indirect inguinal hernia; the swelling on the left side appeared totally confined to his testis and there was an associated hydrocele. Radical orchiectomy was performed on the left side and macroscopically there was an obvious hydrocele sac and a large tumour confined entirely to the epididymis, measuring 14 × 12 × 12 cm. The tumour was a pinkish-white colour, with a firm rubbery consistency and appeared completely encapsulated. Histologically it was a pleomorphic rhabdomyosarcoma. On high power view it was possible to see cross-striations (Fig. 1). Chest X-ray, AFP and β HCG were all normal. No further treatment was given and he remains well 3½ years after presentation.

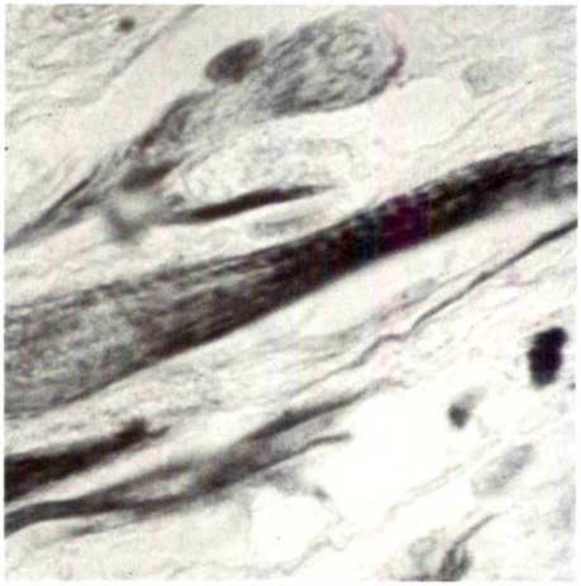

Fig. 1 Cross-striation in rhabdomyosarcoma. (PTAH × 500).

Case 2. A 19-year-old man presented in June 1986 with a rapidly growing, painless right testicular mass extending into his groin over a period of 4 months. Right radical orchiectomy was performed and revealed a white uniform tumour arising within the epididymis and invading the upper pole of the testis. There was an associated hydrocele. Histologically the tumour was an alveolar rhabdomyosarcoma (Fig. 2). Tumour extended along the cord but the proximal limit was clear. CT scan of abdomen and chest showed enlarged left para-aortic lymph nodes. Tumour markers AFP and β HCG were normal. Two months later, repeat CT scan showed widespread metastases within the mediastinium; the lungs remained clear. Eight courses of chemotherapy (Doxorubicin and ifosfamide) were given and after 6 months there was total resolution of all metastases; 2½ years after presentation he remains well and disease-free.

Case 3. An 18-year-old man presented in December 1987 with a 1-month history of a painless mass in his left hemi-scrotum. The mass appeared separate from the testis and confined to the epididymis. This was confirmed at radical orchiectomy. The mass measured 6 × 3 × 3 cm and histo-

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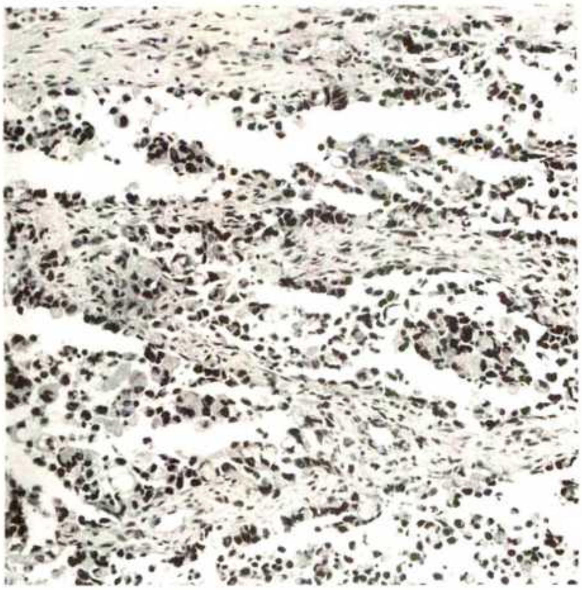

Fig. 2 Alveolar rhabdomyosarcoma. (H and E × 250).

pathology confirmed the tumour to be an embryonal rhabdomyosarcoma. AFP, β HCG and CT scan were normal. He was given 12 courses of adjuvant chemotherapy (cyclophosphamide, doxorubicin, actinomycin D and vincristine) and remains alive, well and disease-free 2 years after presentation.

Case 4. A 20-year-old man presented in October 1972 with a 6-month history of a painless swelling in his right testis. On examination a solid mass measuring 6 × 4 × 4 cm was found confined to the body of the testis; there was a small associated hydrocele. Radical orchiectomy was performed and macroscopically the enlarged testis was almost totally replaced by pale tumour which appeared to arise from the tunica. Histologically it was confirmed as a rhabdomyoscarcoma, with vascular invasion of the proximal limit. Chest X-ray, lymphangiogram and isotope liver scan were all normal. Three weeks after surgery he developed a metastatic left cervical lymph node and despite a course of radical radiotherapy he rapidly deteriorated and died from severe haemolytic crisis, secondary to a rapid dissemination of tumour, 5 months after presentation.

Case 5. A 2½-year-old boy presented in April 1958 with a 3-month history of a swelling in the left testis. A radical orchectomy was performed and showed the testis to be enlarged and totally replaced by firm white tumour confined within the tunica. Histologically the tumour was an embryonal rhabdomysarcoma. No further treatment was given. The child was followed up closely for 10 years and when last seen (21 years after surgery) he remained disease-free and is considered cured.

Case 6. A 3-month-old boy presented when his mother noticed a swelling in his right testis, which had gradually been getting bigger for several weeks. Orchiectomy was performed through a scrotal incision. The testis was completely replaced by a solid yellowish-white tumour which weighed 10 g. Histology confirmed the tumour to be a rhabdomyosarcoma. He received no adjuvant therapy and remained well and disease-free when last seen 21 years following surgery. He is considered cured.

Pathology

The largest tumour in this series reached a maximum diameter of 14 cm (Case 1). Except for Cases 5 and 6, the tumours appeared to have arisen from the paratesticular tissue with or without contiguous tumour spread to the adjacent body of testis. In the last 2 cases, however, the bulk of the tumour lay within the body of the testis itself.

Histologically, Cases 3 to 6 were embryonal variants of rhabdomyosarcoma. The tumours showed a varying degree of differentiation with rhabdomyoblasts and strap cells easily found in Cases 3 to 5. Vascular invasion by tumour cells was noted in Case 4. No other teratomatous elements were present in Cases 5 and 6. Case 2 showed round to oval shaped tumour cells arranged in an alveolar pattern (Fig. 3). Rhabdomyoblasts were abundant. The tumour in Case 1 was composed predominantly of pleomorphic spindle cells arranged in interlacing fascicles. Cross-striations were identified in some of these cells using the phosphotungstic acid-haematoxylin (PTAH) stain (Fig. 1).

Immunohistochemical stains were employed for Cases 1, 2, 3 and 5, all of which stained positively for Desmin, myoglobin and Vimentin (Dakopatts), thus supporting the myoid derivation of the tumours. No chromosomal or DNA studies were carried out, but it is now recognised that the N-myc gene is amplified in alveolar, and N and K-ras gene are amplified in embryonal rhabdomyosarcoma (Stratton *et al.*, 1989; Dias *et al.*, 1990). In addition, the association of rhabdomyosarcoma with the loss of the short arm of chromosome 11 (11p) suggests the involvement of a tumour suppressor gene (Scrable *et al.*, 1989).

Discussion

Intra-scrotal tumours arising from non-germinal origin are very rare, and the majority of those reported arise from paratesticular tissue. Although rhabdomyosarcoma accounts for only 6% of all non-germinal intrascrotal tumours, with an incidence of approximately 1/20 million males per year, it still represents the commonest non-germinal malignant tumour in this site (Elsasser, 1977). It is thought to originate from undifferentiated mesenchyme having the capacity for rhabdomyoblastic differentiation, or perhaps from embryonal muscle tissue that has been displaced during the early stages of tissue development, but not from metaplasia of the connective tissue or smooth muscle.

Rhabdomyosarcoma has been observed in all age groups, but the majority occur either in children or young adults. Approximately 80% occur before the age of 21 years with the remaining 20% evenly spread throughout the remaining decades. There appear to be 2 distinct peaks of increased incidence at 4 years and 16 years (Olney *et al.*, 1979; Hamilton *et al.*, 1989); this is also seen in rhabdomyosarcoma in all other sites and has led some pathologists to postulate a possible hormonal induction for these tumours (Littman *et al.*, 1972). Microscopically, the definitive feature is the presence of rhabdomyoblasts (Fig. 3). Cross-striation, as seen in normal striated muscle, is rarely seen and requires special stains (Fig. 1). Four histological groups are described: pleomorphic, alveolar, embryonal and botyroid. There is no relationship between histological grouping and prognosis and they are of academic interest only.

The clinical presentation tends to include a short history, usually only a few weeks of painless swelling of the scrotum occurring most often in a child or an adult under 21 years. Pain is associated with the tumour in only 7% of cases. Similarly, trauma is associated in only 7% of cases and is not thought to be causative but rather to draw attention to the tumour. The tumour has no preference for the left or right testis or for any particular race. Spread of the tumour is mostly by lymphatics to the iliac and para-aortic nodes, but haematogenous spread does occur, most commonly to the lungs and liver. One-third of patients already have metastases at the time of presentation.

The initial treatment of rhabdomyosarcoma is inguinal orchiectomy. Retroperitoneal node clearance is controversial and is probably not justified for staging or in initial treatment, but it has a role in debulking disease if nodes persist after chemotherapy. The role of chemotherapy and radiotherapy is not fully determined but there is no doubt that the tumour is sensitive to both modes of treatment and certainly adjuvant chemotherapy would now be considered mandatory even in tumours confined to the scrotum (Hamilton *et al.*, 1989). The prognosis of this tumour was considered to be generally poor by Olney *et al.* (1979), their overall survival rate being 68% at 1 year and 30% at 5 years. No patient presenting with metastases survived more than 1 year. Prognosis is now much improved, with a multi-disciplinary approach involving surgery, chemotherapy and radiotherapy. Hamilton *et al.* (1989) reported a 40% survival rate for patients with metastases, for an average of 4.9 years after presentation. Prognosis is generally better if the tumour is confined to the scrotum and in the younger patient.

The present small series is typical in age, presentation and distribution of disease. It also reflects the improving prognosis with the early use of adjuvant chemotherapy, although by far the best results occurred when the tumour arose within the testis; both of these patients have survived for over 21 years and must be considered cured, without any form of adjuvant therapy.

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First Clinical Report of a New Biodegradable Membrane for Use in Urological Surgery

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Summary—Following preliminary *in vitro* and *in vivo* experiments a new collagen Vicryl mesh has been devised. The membrane has been extensively tested in the laboratory and has been found to resist the passage of urine. It holds sutures well and has been shown on an experimental animal to be biodegradable.

The membrane has now been applied in human subjects. It has been particularly efficacious in renal surgery and as a means of sealing a bladder after it has been opened. With respect to the ureter the sealing effect is excellent, to the extent of having produced a urinoma. The membrane has been found to be easily applied in vesicovaginal fistulae but difficulties have been experienced in the presence of infection. It is also an ideal membrane for repair of a urethrovaginal fistula—an area where natural tissues are less easily available.

This is the first recorded use of this new biodegradable membrane in the human subject.

In a preliminary series of experiments a collagen membrane was employed to seal the urinary tract (Gorham *et al.*, 1984; Scott *et al.*, 1986). The simple collagen film, although preventing leakage of urine, was soft and tended to tear easily, thus making suturing difficult. A composite membrane was subsequently developed in which the collagen film was reinforced with Vicryl mesh to form a strong biodegradable composite material which could easily be sutured.

In vitro investigations were carried out to determine the rate of degradation of the material in human urine at different pH values (Gorham *et al.*, 1987), the tendency or otherwise of urinary salts to crystallise on the surface (Gorham *et al.*, 1988) and the ability of urinary tract pathogens to colonise the membrane (Gemmell *et al.*, 1988). As a result of these investigations the composite membrane was deemed suitable for *in vivo* experimentation and was successfully used in rabbits to repair partial nephrectomies (Mohammed *et al.*, 1987; Scott *et al.*, 1988) and to repair full thickness defects in the wall of the urinary bladder (Monsour *et al.*, 1987; Scott *et al.*, 1988).

In addition to being strong and biodegradable, the membrane proved to be haemostatic, showed minimal antigenic response as judged by histopathology, and proved reliable as a sealant. In the case of the kidney, the membrane gave satisfactory haemostasis, prevented leakage of urine and biodegraded in less than 20 weeks, leaving, in the long term, a thickened renal capsule (Mohammed *et al.*, 1987; Scott *et al.*, 1988). When used in repairs of the urinary bladder, the material prevented leakage of urine and was readily replaced by collagenous scar tissue lined with transitional epithelium and with the minimum of shrinkage (Monsour *et al.*, 1987; Scott *et al.*, 1988). A varying degree of regeneration of smooth muscle was also observed within the repair site (Gorham *et al.*, 1989).

It was concluded from these experiments that the new composite membrane could be useful as a repair material in human urinary tract surgery. The use of autologous material, such as omentum, could be avoided.

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We present the first clinical results obtained with a novel type of biodegradable membrane in human urinary tract surgery.

Patients and Methods

Renal operations (n=6)

Three patients underwent partial nephrectomy (1 for tuberculosis, 1 for an apparently benign painful cyst, and 1 for a chronic infection in the upper segment of a duplex kidney). In cases 1 and 2 a biopsy of the wall of the lesion revealed an undiagnosed adenocarcinoma of kidney and nephrectomy was performed 10 days after partial nephrectomy. The third patient was discharged 4 days post-operatively with a perfectly healed wound. Multiple nephrotomies were made (inosine technique) in 3 stone patients to extract fragments of massive staghorn calculi.

Ureteric operation (n=1)

The membrane was sutured around the site of a ureterolithotomy, resulting in mimimum post-operative drainage. However, the patient had persistent pain and ultrasound confirmed the presence of a urinoma. This was managed conservatively.

Bladder operations (n=5)

In 5 cases where the membrane was used as an additional support to cover the suture line in the bladder wall following extensive opening of the bladder, the post-operative drainage was minimal. In 1 male patient a partial cystectomy was performed to remove the posterior wall of the bladder, which had become infiltrated by a small (1.5 cm diameter) adenocarcinoma originating in the large bowel. The catheter became obstructed in the immediate post-operative period and relief of the obstruction led to 500 ml of urine being released from the bladder. There had been no suprapubic leakage during this episode. The suprapubic drain was removed at 3 days and the patient discharged after removal of the urethral catheter at 5 days. A third patient had a vesicocolic fistula secondary to a paracolic abscess resulting from diverticulitis. After a primary resection of bowel the bladder was closed in 2 layers and the fistula site covered with membrane. Post-operatively there was minimal drainage.

Vesicovaginal fistulae (n=3)

The first 2 patients had infected post-irradiation fistulae with a large deficit around which the walls of the bladder were rigid and friable. In both cases membrane was placed across the gap and the patients remained dry for 2 weeks, after which the collagen disintegrated and the fistulae recurred. During this 2-week period, however, the patients were perfectly dry.

The third fistula patient also had infection and post-irradiation changes in the bladder wall. These changes, however, did not prevent relatively easy mobilisation of the bladder epithelium and the vaginal epithelium. Both of these organs were closed by simple sutures with a patch of membrane interposed between the epithelial layers. The patient mobilised easily and quickly and became dry with complete urinary control.

Urethrovaginal fistulae (n=2)

In both cases the membrane was relatively easily applied between a flap of vaginal epithelium and the fistulous opening of the urethra was closed as a primary procedure. In the first case a good repair was obtained. In the second the fistula recurred after the initial repair and required a secondary insertion of membrane. Good progress was made until the patient disrupted the repair by pulling out the catheter with the balloon fully inflated.

In all, 17 patients have now had a piece of the new composite membrane inserted at a variety of different sites within the urinary tract.

Discussion

Urological surgery in developed countries, depending on training and availability of instruments, is now performed using endoscopic or non-invasive procedures such as lithotripsy. There are, however, occasions when it is still necessary to open the urinary tract by conventional surgical techniques. In the post-operative phase, open surgical procedures are complicated by leakage of blood or urine, thus prolonging the period of convalescence. In less well developed countries the degree of sophisticated endoscopic procedures is less well advanced and "open" surgery is still performed on a much greater scale than in modern countries. It is clear that in a time of severe economic stringency it is necessary to minimise the time spent in hospital post-operatively. There is already an advantage in having a biodegradable membrane or suitable prosthesis for the repair of the injured urinary tract.

Collagen, with its high tensile strength, biodegradability and haemostatic properties, its low antigenicity, ability to support cellular growth and its capacity to be reconstituted in a number of physical forms, has already proved to be a substance with several uses in the biomedical field (Chvapil *et al.*, 1973; Huc, 1985; Klopper, 1986; Pharriss, 1980). It has also been suggested that it may be useful in urinary tract surgery (Tanner *et al.*, 1968; Tachibana *et al.*, 1985).

Vicryl (Polyglactin 910) is a water soluble polyester used as surgical suture material and, when woven into a mesh, has shown promising results in other areas of operative surgery (Levasseur *et al.*, 1979; Amory, 1984; Buchsbaum *et al.*, 1985). It was considered that material could be used to reinforce a collagen film to produce a strong composite membrane.

Any artificial material introduced into the human urinary tract should be biodegradable. The current material also has the advantage of being able to prevent calcium deposition (Gorham *et al.*, 1988) and bacterial adhesion (Gemmel *et al.*, 1988). *In vivo* investigations in the urinary bladder have demonstrated regeneration of smooth muscle into the repair site (Monsour *et al.*, 1987; Scott *et al.*, 1988; Gorham *et al.*, 1989). It is possible to use the composite membrane after sterilisation with gamma-irradiation, a method routinely used commercially for medical products, thus making it suitable for use on human subjects.

In the clinical cases recorded thus far the membrane has proved ideal for the closure of the partially nephrectomised kidney and the minimal leakage of blood and urine has reduced the time of post-operative drainage. When used to cover nephrectomy incisions the membrane is surgically easy to handle and has properties which allow good sealing at a site of leakage of both blood and urine. Perhaps it is paradoxical that the membrane is so effective in containing urine that, in the 1 ureteric operation, drainage of the inevitable leakage of urine was contained between the periureteric wall and the membrane and resulted in the formation of a urinoma.

With respect to bladder surgery the membrane is ideal for covering a cystotomy. The major problem in bladder work occurs when the membrane by itself has been used to fill the gap created in post-irradiation fistulae. From our animal work (Mohammed *et al.*, 1987; Monsour *et al.*, 1987; Scott *et al.*, 1988) we could reasonably have expected urothelium to cover the collagen. However, in the 2 human subjects where the membrane by itself was used to cover the defect there was insufficient time for this process to be completed because of the rapid biodegradation of the collagen layer of the membrane. It is expected that, by increasing the degree of cross-linking, the duration of biodegradability can be extended to allow full cover by transitional epithelium to take place.

In conclusion, in addition to its advantages in urinary tract surgery, the membrane can be easily sterilised and packaged, thus making it readily available for use in emergency and elective urological surgery.

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PAEDIATRIC UROLOGY

Fluoride Metabolism and Fluoride Content of Stones from Children with Endemic Vesical Stones

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Summary—Twenty children with endemic vesical stones showed normal plasma and urinary excretion of fluoride on a mean fluoride intake of 2.5 ± 0.8 mg/24 h. The mean fluoride content of the stones obtained from these children was 315.6 ± 264.9 µg/g in the nucleus and 229.9 ± 212.8 µg/g in the periphery (this was not statistically significant). Calcium-containing stones had a higher fluoride content than stones containing uric acid and ammonium urate. It was concluded that children with endemic vesical stones have normal fluoride metabolism. Trace quantities of fluoride present equally in the nucleus and peripheral parts of the stones suggest that fluoride does not cause initiation or growth of the nucleus of vesical stones and is adventitiously deposited with calcium salts in these stones.

Fluorosis and endemic vesical stones are widely prevalent in several parts of the world and mostly affect the rural farming communities where ground water is the main source for drinking purposes (Teotia and Teotia, 1977; Teotia *et al.*, 1979). The artificial fluoridation of water in several parts of the world is likely to increase the fluoride intake. We therefore studied fluoride metabolism and the fluoride content of endemic vesical stones in order to find out if fluoride plays a role in the causation of endemic vesical stones.

Patients and Methods

A total of 20 children with endemic vesical stones and 20 normal controls matched for age, sex and socio-economic status were admitted to the Metabolic and Endocrine Wards of the LLRM Medical College and Associated SVBP Hospitals, Meerut, India, for clinical, nutritional, biochemical and radiological evaluation.

Fasting blood plasma and 24-h urine samples were collected from every child for 3 days, and a sample of their drinking water was also obtained. All 20 stones removed surgically from these children were subjected to complete chemical and X-ray diffraction analysis, including their fluoride content.

The water was analysed for pH, hardness, calcium, magnesium, chloride and fluoride. Blood plasma was analysed for calcium, phosphorus, alkaline phosphatase, urea, uric acid, creatinine and fluoride. The 24-h urine samples were analysed for calcium, phosphorus, oxalate, uric acid, creatinine and fluoride using standard methods (Teotia *et al.*, 1983). Fluoride analysis of the specimens was done by using an F^- ion electrode and a PHM64 Research Radiometer (Singer *et al.*, 1969).

Qualitative chemical analysis of the vesical stones was performed according to the method of Hodgkinson (1971). The periphery and nucleus of the stones were analysed separately by the X-ray diffraction method. The diffusion method was used to assay the fluoride content. The principle of this method requires digestion and acidification of the sample with a suitable acid. Gaseous hydrogen fluoride is formed and trapped in an alkaline solution. A microdiffusion cell similar in design to that described by Conway (1963) was employed. After the acidification and digestion were completed the solutions were qualitatively transferred

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to a 5-ml volumetric flask and diluted to volume with double distilled water. The cell potential was then measured using an Orion 94 series fluoride sensitive electrode together with a 90 series sleeve type Ag/AgCl reference electrode. Fluoride concentrations were determined from previously constructed calibration curves.

Results

Twenty children with endemic vesical stones and 20 normal controls were studied (Table 1). The children with endemic vesical stones had characteristic clinical symptoms and radiological evidence of stone in the bladder. Ground water obtained through hand pumps was consumed by both groups of patients for drinking and household purposes. Each house had its separate source of water, which was collected and analysed. No statistically significant difference was seen in any of the constituents analysed in water consumed by normal children and by those with endemic vesical stones (Table 2).

Table 1 Details of Patients

Group	*No of patients*	*Mean age (years)*	*Sex*	
			M	*F*
Endemic vesical stone	20	5.8 (2–9.2)	19	1
Control	20	6.0 (2–9.8)	18	2

The mean dietary fluoride intake of children with stones was 2.5 ± 0.8 and in controls 2.8 ± 0.6 mg/24 h. This difference was not statistically significant (Table 3).

Plasma biochemical findings and the urinary excretion of calcium, phosphorus, magnesium, oxalate and creatinine were similar in controls and in children with stones. Plasma and urinary fluoride excretion was comparable in both groups but 24-h urinary uric acid excretion was significantly elevated in children with endemic vesical stones (Tables 4, 5, 6).

Calcium oxalate and ammonium urate formed the major constituents of the vesical stones (Table 7); apatite was present in 8, magnesium ammonium phosphate in 7, uric acid in 4, and traces of uncombined elements of calcium and ammonia were present in 16.

The mean fluoride content in the nucleus and periphery of the stones was 315.6 ± 264.9 and 229.9 ± 212.8 µg/g respectively. This was not statistically significant ($P = 1.10$).

X-ray diffraction analysis of the major chemical components was done separately for the nucleus and periphery of the stones and showed that 7 stones had ammonium urate and 6 had more than 1 component in the nucleus. Eight stones had calcium oxalate, 3 had ammonium urate and 4 had uric acid as major constituents in the periphery. Correlation of the fluoride content with the major

Table 2 Chemical Composition of Drinking Water (mg/l)

	Endemic vesical stone group	*Controls*
pH	6.0±0.3 (5.7–6.3)	6.2±0.2 (6 0–6.4)
Total hardness	218 0±44.5 (158.5–264.5)	220 0±36.2 (185.6–256.2)
Total acidity	38 8±7.2 (30.6–45.9)	36 2±5 8 (30.8–42 0)
Total alkalinity	265.8±25.6 (240.2–290 0)	260.5±21.9 (239 6–282 5)
Calcium	56.5±20.2 (36.8–76 2)	60.2±0.2 (54 2–75.8)
Magnesium	15.6±3.2 (15.2–18.9)	15.0±3.7 (11 2–18.6)
Chloride	49 5±7.8 (42.2–57.2)	44.5±8 2 (36.8–52.8)
Fluoride (ppm)	0.7±0.0 (0.6–0.8)	0 6±0 1 (0.5–0.7)
Iodine (µg/l)	13.6±2.3 (11.2–15 9)	8.5±1.8 (6.7–10 3)

Table 3 Daily Dietary Intake

	Calories	Protein (g)	Calcium (mg)	Oxalate (mg)	Fluoride (mg)
Endemic vesical stone group	1006±250 (800–1250)	20.8±7.3 (13.2–28.2)	486.0±30.5 (455.2–505.8)	34.7±18.3 (24.2–52.6)	2.5±0.8 (1.6–3.8)
Controls	1002±180 (920–1180)	22.4±9.5 (14.6–31.5)	409±42.2 (372–451)	32.6±6.2 (26.5–38.6)	2.8±0.6 (2.0–3.9)

Table 4 Plasma Biochemistry

	Fluoride (μmol/l)	Calcium (mmol/l)	Phosphorus (mmol/l)	Alkaline Phosphatase (KA Units/dl)	Urea (mmol/l)	Uric acid (mmol/l)	Creatinine (mmol/l)
Endemic vesical stone group	0.5±1.2 (0.2–1.7)	2.4±0.1 (2.3–2.5)	1.5±0.1 (1.4–1.6)	15.2±2.3 (9.8–17.2)	4.1±0.5 (3.6–4.7)	0.2±0.03 (0.1–0.2)	0.05±0.02 (0.03–0.07)
Controls	0.4±1.2 (0.3–1.9)	2.4±0.1 (2.3–2.5)	1.5±0.2 (1.3–1.7)	14.6±1.7 (12.0–16.2)	3.8±0.5 (3.3–4.3)	0.2±0.02 (0.1–0.2)	0.04±0.01 (0.03–0.06)

Table 5 Urinary Excretion

	Volume (ml/24 h)	pH	Ammonia (mmol/day)	Uric acid (mmol/day)
Endemic vesical stone group	593.0±106.7 (485.0–695.8)	6.0±0.2 (5.8–6.2)	27.7±9.3 (18.1–37.0)	2.3±0.5 (1.7–2.7)
Controls	547.0±167.2 (398.3–708.9)	6.1±0.3 (5.8–6.4)	21.1±9.6 (11.5–30.3)	1.5±0.05 (0.7–2.6)

Table 6 Urinary Excretions (mmol/24 h)

	Calcium	Phosphorus	Magnesium	Oxalate	Fluoride
Endemic vesical stone group	2.6±1.0 (1.7–3.5)	12.0±0.5 (11.5–12.4)	3.3±0.4 (2.9–3.8)	0.2±0.1 (0.1–0.4)	0.07±0.02 (0.05–0.09)
Controls	2.4±1.0 (1.1–4.8)	10.9±0.5 (8.7–14.5)	3.7±0.2 (3.2–4.3)	0.2±0.1 (0.1–0.3)	0.08±0.01 (0.07–0.09)

chemical component in the nucleus and periphery showed no statistically significant differences (Table 8). The fluoride content was highest in the nucleus and outer part of stones with calcium oxalate as the major component and lowest in stones with uric acid as the major component.

Discussion

The finding of normal plasma and urinary biochemistry and raised uric acid excretion in children with endemic vesical stones is consistent with earlier reports and may be due to delayed maturating mechanisms for renal tubular reabsorption of uric acid. The whole wheat consumed as staple food by these children further increases saturation and precipitation of uric acid. Transient periods of dehydration and acidosis due to diarrhoea, infection and other febrile illnesses would cause the excretion of concentrated acidic urine with increased production of ammonia, and precipitate ammonium urate, uric acid or calcium oxalate and initiate the nucleation of a stone. However, such an episode in clinical practice may go unnoticed until the stones

Table 7 Chemical Analysis of Vesical Stones (g/100 g)

	Calcium oxalate	*Magnesium ammonium phosphate*	*Apatite*	*Ammonium urate*	*Uric acid*	*Uncombined elements*	
						Calcium	*Ammonia*
Mean	23.3	1.8	5.6	40.4	4 3	1.0	9.0
S.D.	±16.9	±1.57	±14 2	±22.7	±9.7	±1.1	±8.6
Range	2.8–48 6	0.0–12 0	0.0–51.9	4 4–66.6	0.0–31.6	0 3–3 5	0 0–34.9

Table 8 Fluoride Content in Relation to Chemical Component of Vesical Stones

Component (X-ray diffraction)	*No*	*Fluoride content (nucleus) (μg/g)*	*No*	*Fluoride content (periphery) (μg/g)*	*t value*	*P*
Calcium oxalate monohydrate	5	568.3±376.4	8	375.4±233	1.06	Not significant
Ammonium acid urate	7	193.5±116 1	3	158.3±49.1	0.49	Not significant
Uric acid	2	151.0±144.9	4	81 7±59 2	0.9	Not significant
Mixed component*	6	284.8±210.3	3	240.7±274.7	0.2	Not significant

* Calcium oxalate monohydrate combined with uric acid, ammonium acid urate or struvite.

become big enough to cause symptoms (Teotia *et al.*, 1981).

The normal dietary intake, plasma and urinary excretion of fluoride indicate that fluoride metabolism is not disturbed in children with endemic vesical stones. The trace quantities of fluoride found in these stones is adventitiously deposited with calcium salts. Because of the strong affinity of fluoride for calcium, the highest fluoride content was detected in stones with calcium oxalate as their major component and in stones of mixed composition. The similarity between the fluoride content of nucleus and periphery suggests that fluoride does not play a part in the initial nucleation of these stones.

Reports in the literature on the role of fluoride in the causation of calcium oxalate stones are controversial. The administration of fluoride to rats has been reported to cause crystalluria and an increased incidence of stones (Das, 1982). A high incidence of urinary tract calculi from high fluoride areas in India has been reported by Jolly *et al.* (1980). On the other hand, several reports indicate the negative role of fluoride in the causation of kidney stones. Venkateswarlu *et al.* (1958) observed a slightly lower frequency of urinary stones in rats on a stone-inducing diet and 10 ppm fluoride in the drinking water compared with control rats on a similar diet but no supplemental fluoride. An inhibitory role of fluoride in ethylene glycol-induced calcium oxalate stone formation and delay in the dose and the time-dependent initiation of calcium oxalate nucleation and the formation of smaller crystals in rats has been reported by Hering *et al.* (1984). The fluoride content was higher in predominantly calcium-containing stones in fluoridated areas than in non-fluoridated areas (Hesse *et al.*, 1978). In other types of stones, *e.g.* uric acid and cystine, there was no statistically significant difference in their fluoride content in fluoridated and non-fluoridated areas. The fluoride content of urinary and biliary tract calculi is not affected by the level of fluoride intake according to a study in which renal calculi from high and low fluoride areas were compared (Zipkin and Leone, 1958). Herman *et al.* (1958) examined the fluoride content of human tissue from 38 cases of urolithiasis and found no evidence to suggest that fluoride, in the amounts ingested by the patients, was toxic to the kidneys.

The normal fluoride metabolism of children in the present study, together with trace quantities of fluoride present equally in the nucleus and the periphery on stone analysis, strongly suggest that fluoride does not cause either initiation or growth of the nuclei. The relatively higher content of fluoride in stones with calcium oxalate as the major constituent suggests that fluoride is deposited as a result of the strong affinity of this halogen for calcium.

Studies of children living in endemic areas for fluorosis since birth have shown that prolonged ingestion of high amounts of fluoride does not alter the urinary and plasma biochemistry to make it conducive to stone formation (Teotia *et al.*, 1984). The absence of stones on plain abdominal X-rays of 200 children with proven endemic skeletal fluorosis support our finding that fluoride does not play a role in the nucleation or growth of endemic vesical stones and is deposited adventitiously with calcium in these stones.

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British Journal of Urology (1991), **68**, 430–439

Case Reports

Bilateral Testicular Secondaries from Transitional Cell Carcinoma of the Bladder

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Testicular secondaries are uncommon but secondaries from transitional cell carcinoma (TCC) of the bladder are rare. We report the sixth case in the English literature.

Case Report

A 67-year-old man presented in July 1985 with a short history of haematuria. Clinical examination was unremarkable; an IVU showed no abnormality in the upper urinary tracts. At cystoscopy there was an area of flat tumour on the anterior wall of the bladder with extension to the lateral walls. Histology revealed a poorly differentiated TCC (T1). Despite intracavity doxorubicin and subsequent radiotherapy there was endoscopic evidence of tumour recurrence by May 1987. A CT scan and lymphangiogram showed no evidence of pelvic or distant tumour spread and he was therefore admitted with a view to salvage cystectomy. At this stage he was noted to have a painful swollen left testis with an associated hydrocele and marked induration of the spermatic cord. A right hydrocele was also present, but after aspiration of 200 ml of straw coloured fluid the testis was normal to palpation, although cytology detected dyskaryotic cells. A left orchidectomy was performed via an inguinal approach. Histology confirmed metastatic TCC infiltrating the testis, epididymis and spermatic cord with tumour at the resection margin. Consequently, salvage cystectomy was abandoned. He returned 3 months later with pain and similar changes on the right side. This was also managed by orchiectomy, the histology showing a similar appearance.

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Meconium Vaginalitis

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Meconium peritonitis is a form of chemical peritonitis resulting from *in utero* perforation of the gastrointestinal tract and may occur as early as 24 weeks of fetal life (Heydenrich and Marcus, 1976). The meconium that is spilled into the peritoneal cavity may traverse a patent processus vaginalis into the vaginal cavity and be confused with intrauterine torsion or a testicular tumour.

Since Olnick and Hatcher (1953) described the first case of meconium vaginalitis in 1953, approximately 20 cases have been reported.

Case Report

A 2-month-old baby was seen as an emergency with a right scrotal mass. Initially diagnosed as an acute scrotum, possibly a testicular torsion, right orchiectomy was performed.

On sectioning the surgical specimen, an apparently normal gonad and epididymis were identified, with a significantly widened vaginal space occupied by lax tissue with microcalcifications (Fig. 1). Microscopically, the vaginal tissue was fibroblastic and myxoid with an accumulation of a calcific, amorphous material in which cellular debris and keratin were identified; there were aggregates of haemosiderin and bile pigments in the connective tissue. These findings led to a diagnosis of meconium vaginalitis.

Retrospectively, we determined that the baby was the product of a normal, full-term pregnancy. Fetal ascites had been diagnosed sonographically at 35 weeks' gestation, disappearing on a subsequent sonogram at 37 weeks. At birth he had a weight of 6.71 pounds and an Apgar score of 10. The scrotum was described as enlarged, but soft, being diagnosed as a bilateral hydrocele.

Twelve hours before presenting as an emergency, the

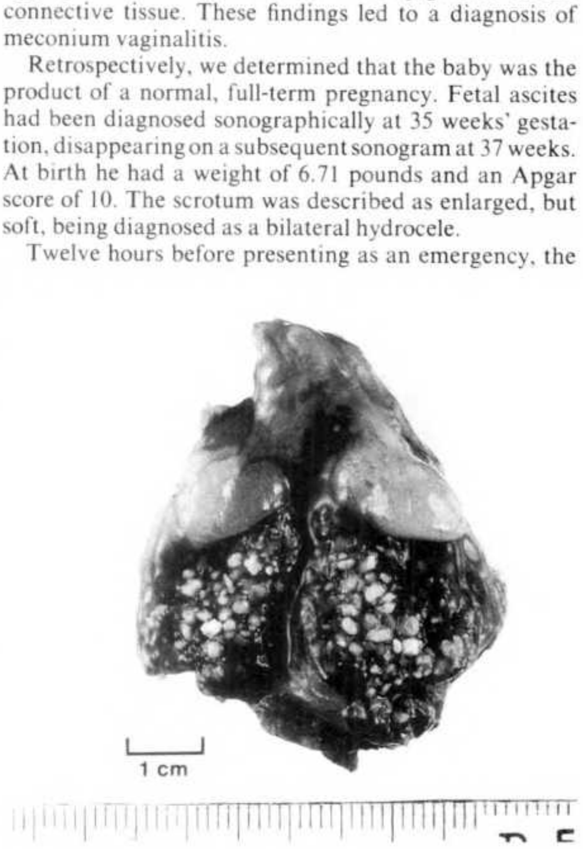

Fig. 1 Section showing preservation of the testis and lax tissue with vaginal microcalcifications.

baby had a fit of crying that motivated a visit to the paediatrician, who, upon examination, found a right intrascrotal mass.

Post-operatively, the contralateral scrotum was noted to be enlarged and contained extratesticular calcifications. Intra-abdominal calcifications were also identified (Fig. 2). After a satisfactory post-operative course, abdominal and scrotal X-rays performed 1 month later revealed disappearance of the abdominal calcifications and a reduction in the left scrotal calcifications. Further evaluation 6 months post-operatively showed the patient to be progressing satisfactorily.

Comment

The development of meconium vaginalitis occurs only after the prior onset of meconium peritonitis. According to Fries and Talbot (1955), meconium peritonitis is a chemical peritoneal inflammation secondary to an intestinal perforation that spills meconium (formed by desquamated epithelial cells, bile, lipids and mucin) into the peritoneal cavity. Peristaltic activity and meconium must be present for this to occur (Olnick and Hatcher, 1953); thus it is a disease that will have its onset, at the earliest, around the 24th week of gestation.

Clinically, there are 2 forms of meconium peritonitis. One is serious and usually fatal, and the other is mild and self-limiting (Lange, 1964).

According to Vordemark (1984), 90% of neonates have a patent processus vaginalis which permits liquid meconium to reach the vaginal cavity. The child is born with a hydrocele. Subsequently, the enlarged scrotum gradually becomes more solid and calcifications appear.

The clinical picture, especially the radiological signs (Friedman *et al.*, 1983), showing intra-abdominal and scrotal calcifications, are enough to make the diagnosis of meconium vaginalitis.

If the diagnosis has been made with certainty, surgical exploration need not be performed (Thompson *et al.*, 1973), as the disease progressively disappears (Berdon *et al.*, 1967).

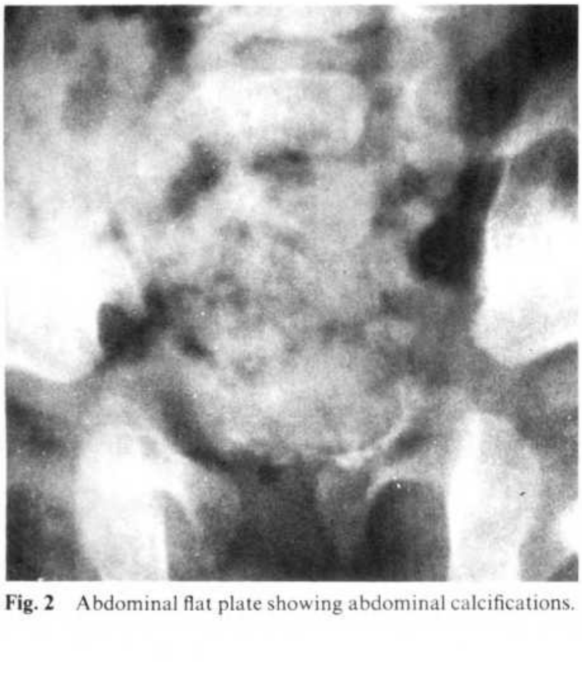

Fig. 2 Abdominal flat plate showing abdominal calcifications.

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Stone Formation on Ureteric Stents in Children

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The use of indwelling ureteric stents, either as definitive treatment for obstructive uropathy or as a temporary adjunct to urinary tract surgery, has been increasing in the last few years. We have used it to support renal tract surgery for varying pathological conditions in which post-operative stricturing, particularly at the vesicoureteric junction, might occur. We have also tried to use such stenting in an attempt to treat a minor degree of obstruction, with a few complications. However, 3 patients have developed calculi associated with their stents.

Case Reports

Case 1. This non-ambulating 13-year-old girl was born with myelomeningocele and hydrocephalus. Bilateral hydronephrosis with bilateral vesicoureteric reflux was demonstrated in the neonatal period. Recurrent infections developed and led to bilateral ureteric reimplantation at the age of 10 years. Following this she was well for 2 years, when persisting infection was found associated with a right renal and 2 vesical calculi. The latter were removed cystoscopically. Two months later she was found to have a stone in the lower end of the left ureter with progression of the dilatation on this side. The stone was removed through a ureterotomy and the vesicoureteric junction explored and found to be stenosed. The ureter was closed over a double pigtail silicone stent BARD and she continued on prophylactic antibiotics. Seven weeks later she presented with abdominal pain and a straight X-ray of the abdomen revealed a stone around the ureteric stent. Renal ultrasound revealed improvement of the upper tract dilatation. It proved impossible to remove the stent with the stone endoscopically, so both were removed at open operation (Fig.). Throughout her life serum electrolytes, blood urea and serum creatinine had remained normal. The stone comprised ammonium, calcium, phosphate, carbonate and oxalate.

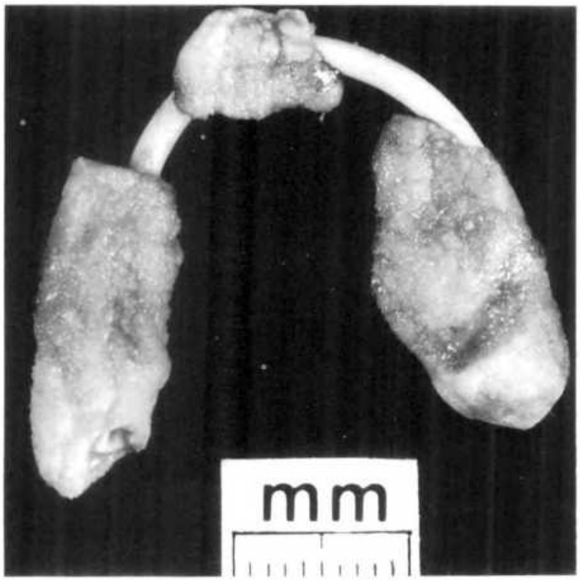

Fig. Encrusted stent from Case 1.

Case 2. This boy was diagnosed at the age of 6 months as suffering from posterior urethral valves, without vesicoureteric reflux but with bilateral upper tract dilatation. He underwent endoscopic resection of the valves but continued to have recurrent symptomatic urinary tract infection with progression of upper tract dilatation. At 7 years of age a DTPA renogram revealed significant bilateral obstruction and bilateral trimming and reimplantation of the ureters was undertaken. This was complicated by vesicoureteric obstruction which was relieved by bilateral Y-type ureterostomies, but the right kidney deteriorated, became non-functioning and was removed. At the age of 10 a siliconised double pigtail stent was inserted into the remaining renal tract, prior to closure of the stoma. Three months later he was found to have stones on both the upper and lower ends of the ureteric stent which could not be removed endoscopically. The stones and the stent were removed at open operation. Since that time he has remained free of infection and his upper tract dilatation has improved. The composition of the stone was calcium, magnesium, ammonium and phosphate.

Case 3. This girl presented at the age of 6 months with recurrent urinary tract infection and was found to have a right ectopic ureterocele on a single ureter. Excision of the ureterocele was performed at 8 months with bilateral ureteric reimplantation. She failed to attend for follow-up until 5 years old, when she complained of continuing incontinence. Ultrasound revealed a normal right kidney but a hydronephrotic left kidney and urodynamic studies indicated a small capacity bladder with uninhibited high pressure detrusor contractions. A left to right transuretero-ureterostomy was performed and ileal patch cystoplasty. A silicone double pigtail stent was left through the ureteric anastomosis. Two months later, at removal of the stent, it was found to be encrusted and analysis of the stone revealed the presence of ammonium, magnesium, carbonate, phosphate and oxalate.

All 3 patients were screened for metabolic causes of stone formation, but none was found.

Comment

Double pigtail ureteric stents have been recommended for a variety of obstructive lesions of the urinary tract and to support various forms of surgery with encouraging results (Pocock *et al.*, 1986). Although some catheters have been left *in situ* without complication for periods of 12 months, the manufacturers generally recommend removal after 6 months. Most experience has been gained in the management of adult patients and the formation of stones has been reported (Spirnak and Resnick, 1985; Gordon, 1989; Rhind, 1989). The cases reported here indicate that despite the absence of biochemical causes for stone formation, the presence of a foreign body and bacteria may lead to stone formation on implanted stents. In 2 of these cases the stones were of such a size and irregularity that endoscopic removal was not possible. It is therefore wise to X-ray all such stents prior to endoscopic removal.

Acknowledgement

We are grateful to Mrs A. Jones for typing this manuscript.

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Bladder Calculus Causing Vesicovaginal Fistula in Pregnancy

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Case Report

A 20-year-old primigravida was referred with an unconfirmed diagnosis of renal failure and suspected premature rupture of fetal membranes. She had a 2-year history of lower abdominal pain, frequency of micturition and dysuria, which had been getting worse during this pregnancy. She also felt a mass moving in the pelvis which had obstructed her urinary flow, causing severe pain and hesitancy. Plain X-ray showed a large calcified mass in the bladder (Fig. 1) and intravenous urography revealed bilateral hydronephrosis and hydroureter. One day before referral she developed leakage of foul-smelling fluid *per vaginam*. Since then she stopped having frequency of micturition and her pain became localised in the suprapubic region.

On abdominal examination the fundal height corresponded to 32 weeks' gestation. The fetus was lying longitudinally, cephalic presentation. Fetal heart rate was 140/min and regular. On vaginal examination there was evidence of drainage of foul-smelling urine through a vesicovaginal fistula approximately 0.5 cm in diameter at the mid-anterior vaginal wall. A hard calculus protruded through it.

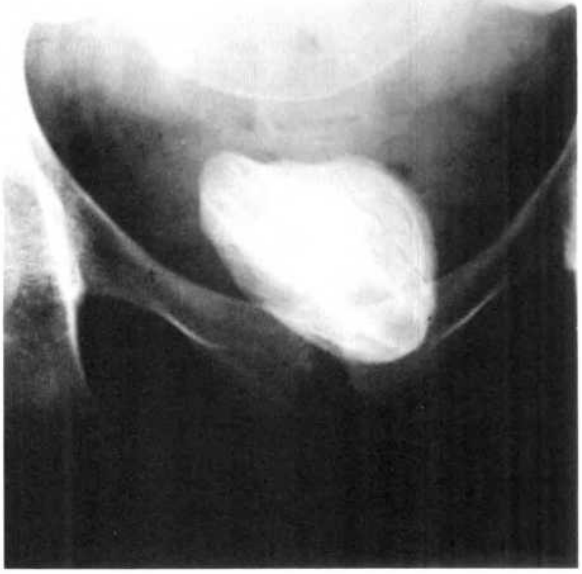

Fig. 1 Plain X-ray showing large bladder calculus.

She was managed conservatively with antibiotic cover for 4 weeks. On the fifth week after admission lower uterine segment caesarian section was done and a male baby weighing 2450 g delivered with good Apgar scores 8 at 1 min, 10 at 5 min. The placenta was delivered, the uterus was closed in 3 layers and haemostasis was achieved. The bladder was then opened by a midline incision and an 80-g calculus was removed (Fig. 2). The bladder was found to be grossly oedematous. A circular fistula 2 cm in diameter was found at the base, near the

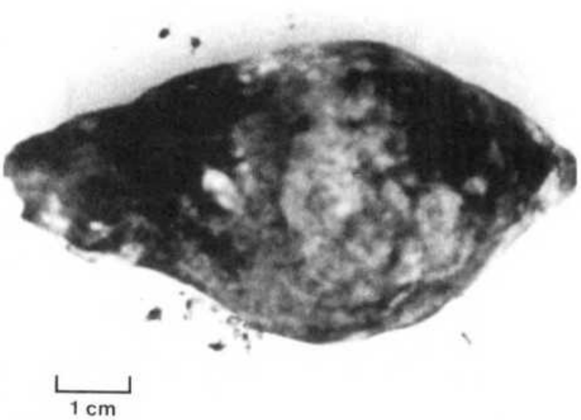

Fig. 2 Bladder calculus weighing approximately 80 g.

urethra. Sharp dissection was done and the vaginal wall was separated from the bladder wall. Each wall was sutured with 2/0 chromic catgut. The omentum was placed between the 2 sutured layers and secured.

Comment

Coe *et al.* (1978), Cumming and Taylor (1979) and Lattanzi and Cook (1980) reported independently that the course of urolithiasis is not affected by pregnancy, although urinary tract infection is more common in such patients. Management depends on gestation. Stones detected at early gestation may be removed with little fear of interrupting pregnancy. When calculi are symptomatic or associated with infection or impairment of renal function, they may have to be removed urgently. Our patient had normal renal function tests and there was no need for immediate intervention. The fistula was caused by the sharp edge of the bladder calculus, presumably pressed between the advancing fetal head and the pubis through the bladder and vaginal walls.

If possible, large bladder calculi which may cause severe soft tissue damage and dystocia during labour should be removed during pregnancy either transurethrally or by suprapubic cystostomy. Our patient underwent removal of the calculus by suprapubic cystostomy at the same time as caesarian section and repair of the vesicovaginal fistula.

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Basal Cell Carcinoma of the Scrotum—A Rare Clinical Entity

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Basal cell carcinoma (BCC) of the scrotum is a rare disease which, because of its less aggressive character, must be differentiated from the more common squamous cell carcinoma (SCC). Two cases of basal cell carcinoma of the scrotum are presented and the literature is reviewed.

Case Reports

Case 1. A.W., a 70-year-old retired subpostmaster, presented with a 5-month history of an ulcer on the right side of the scrotum. This lesion had initially gradually increased in size, but appeared to have been static over the last 2 months. Although 40 years previously he had worked briefly as a car mechanic, the patient denied any exposure of the scrotum to industrial oils or chemicals.

Physical examination revealed a 1-cm ulcer with raised, rolled edges, induration and peripheral erythema. A 3-mm satellite nodule lay adjacent to the larger lesion. No enlarged inguinal nodes were palpable.

The lesion was excised with a 1.5 cm margin of normal skin. There was no evidence of recurrence 9 months after operation. Histological examination showed a lesion characteristic of BCC.

Case 2 H.H., a 72-year-old retired mechanical engineer, presented with a 7-month history of a slowly enlarging ulcer on the left hemiscrotum. Seven years previously he had undergone excision of BCC from the right upper canthus.

Physical examination revealed a nodular ulcer 0.6 cm in diameter, with some peripheral erythema. The inguinal nodes were not enlarged.

The lesion was excised with a 1-cm margin of normal skin. Histology showed a nodular lesion with focal ulceration and features of BCC, with peripheral cell palisading. The edges of resection were clear of tumour.

There was no evidence of recurrence 2 years after operation, although 9 months after excision of the scrotal lesion a further BCC was removed from the right cheek.

Comment

Scrotal carcinomas are uncommon, with an estimated annual incidence of 0.1/100,000 (Clemmesen, 1964). The majority are squamous lesions and only 5 to 7% are BCCs (Kickham and Dufresne, 1967; Ray and Whitmore, 1977). Only 15 cases of BCC of the scrotum have been documented in the world literature (Grossman and Sogani, 1981; Greider and Vernon, 1982; McDonald, 1982; Gerber, 1985).

In contrast to SCC, BCC is usually of low malignancy. However, there are reports of BCC arising from the scrotum and progressing to proven metastatic disease, with a delay of 4 years (Hughes, 1973) and 13 years (Richter, 1957).

A review of the literature shows that the prognosis of BCC originating in the scrotum is much better than that of SCC. Wide excision alone is usually curative, but this tumour does have the potential to metastasise. Close attention must therefore be paid to the detailed history of the primary lesion, and prolonged follow-up is indicated if the tumour has aggressive characteristics.

Acknowledgements

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Pleural Effusion Associated with Urinary Extravasation due to Renal Colic

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Case Report

A 78-year-old woman was admitted with a 2-week history of epigastric and severe left lumbar pain associated with nausea and vomiting. Her past history was unremarkable.

On examination she had a normal abdomen with marked tenderness over the left flank. Blood analysis, renal and hepatic tests and ECG were normal. Urine analysis revealed microscopic haematuria.

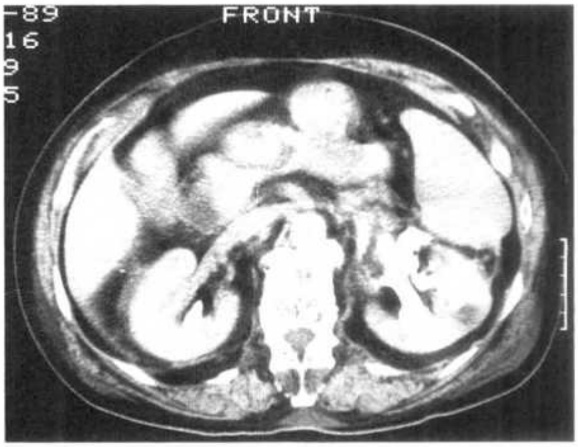

Fig. CT scan at L2 level demonstrating extravasation of contrast medium from the left middle and lower renal calices.

A plain KUB showed a left ureteric calculus and chest X-ray revealed a pleural effusion on the left side. Following the parenteral use of analgesics, intravenous urography showed a normal right kidney and a hydronephrotic, poorly defined left kidney with extravasation of contrast medium. A CT scan confirmed hydronephrosis and extravasation of dye from the middle and lower renal calices (Fig.).

The ureteric stone was passed spontaneously the next day and the patient was asymptomatic when she left hospital 3 days after admission. The pleural effusion disappeared 10 days later.

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Megalourethra

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Megalourethra is a rare congenital anomaly characterised by a failure of development of erectile tissue and subsequent dilatation of the penile urethra. The term was first used by Nesbitt (1955) and since then many of these defects concerning the corpus spongiosum and the corpora cavernosa have been reported (Mortensen *et al.*, 1985; Appel *et al.*, 1986; Aigen *et al.*, 1987).

Concomitant malformations, which are sometimes incompatible with survival, have important implications for therapy and prognosis. Associated anomalies may involve the urinary tract (renal hypoplasia, ureterohydronephrosis, megaureter, megacystis, reflux, bladder diverticula, hypospadias, manifestations of intersex, urethral valves, prune belly syndrome) as well as other organs (teeth, heart, intestines).

Case Report

A male infant was delivered by caesarean section after a normal pregnancy. Post-natal examination showed no abnormality in the urogenital region. Spontaneous micturition with a forceful stream was present from birth. After some days the infant developed a non-irritating, plum-sized swelling on the proximal ventral shaft of the penis (Fig. 1).

After aspiration of 14 ml of clear yellowish fluid the patient developed oedema and reddening of the external genitalia (Fig. 2) accompanied by fever. Urine culture revealed *Klebsiella*. Upper abdominal ultrasound demonstrated moderate bilateral ureterohydronephrosis.

A suprapubic catheter was inserted and the scrotum was drained. Antibiotics were administered.

After control of the infection, the voiding cystourethrogram (Fig. 3) revealed a sac-like dilatation of the penile urethra without infravesical obstruction and grade II reflux on the right side. Surgical revision was carried out using a 2-stage procedure and was completed after 4 months, when the patient was growing and developing well: after initial marsupialisation of the urethra by incision and degloving the penile skin to the base of the phallus, a new urethral tube was formed in a second-stage procedure (Figs 4, 5, 6).

Histological specimens of the expanded urethra contained no spongy tissue, the urethral epithelium lying upon the fibrous wall of the tunica albuginea.

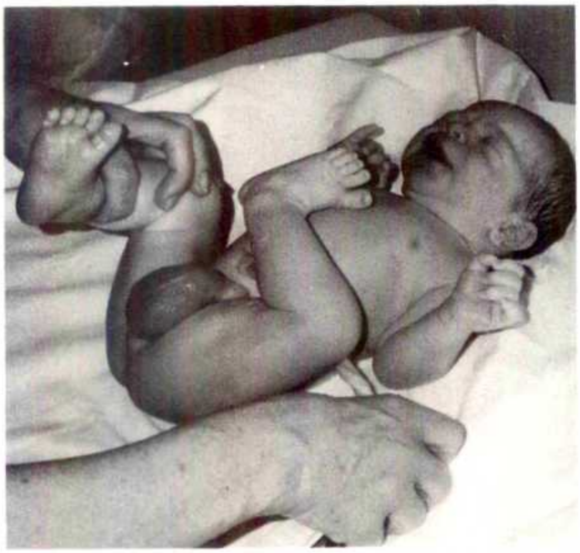

Fig. 1 Neonate with swelling on the proximal ventral shaft of the penis.

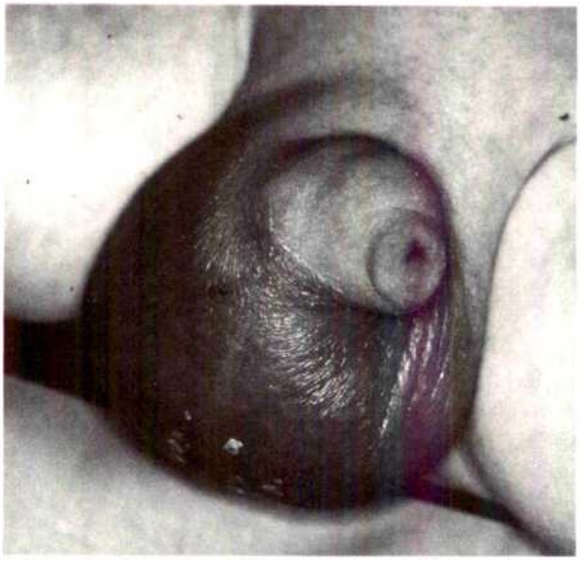

Fig. 2 Oedema and local infection after trans-scrotal puncture of the swelling.

Comment

The term magalourethra represents a spectrum of defects caused by incomplete differentiation of the corpus spongiosum and the corpora cavernosa due to an embryogenic arrest at about 7 weeks of gestation.

During normal embryonic development the anterior segment of the cloaca develops into the urethral groove, which closes to form the urethra and connects with the ectodermal ingrowth of the glandular part. It is characteristic of megalourethra that the urethra is insufficiently covered by mesodermal vascular connective tissue. This embryogenic defect permits the balloon-like dilatation of the distal urethra, mostly without mechanical obstruction of the lower urinary tract. In contrast to hypospadias (with chordee and ventral curvature), megalourethra may be accompanied by dorsal deviation of the penis (Nebitt, 1955; Stephens, 1983).

This anomaly can be divided into scaphoid and fusiform types according to its extent and physical appearance. The scaphoid variety is more frequent and characterised by the absence or incomplete formation of the corpus spongiosum. Examination of histological sections shows a normally formed urethra, normal penile skin and Buck's fascia. The

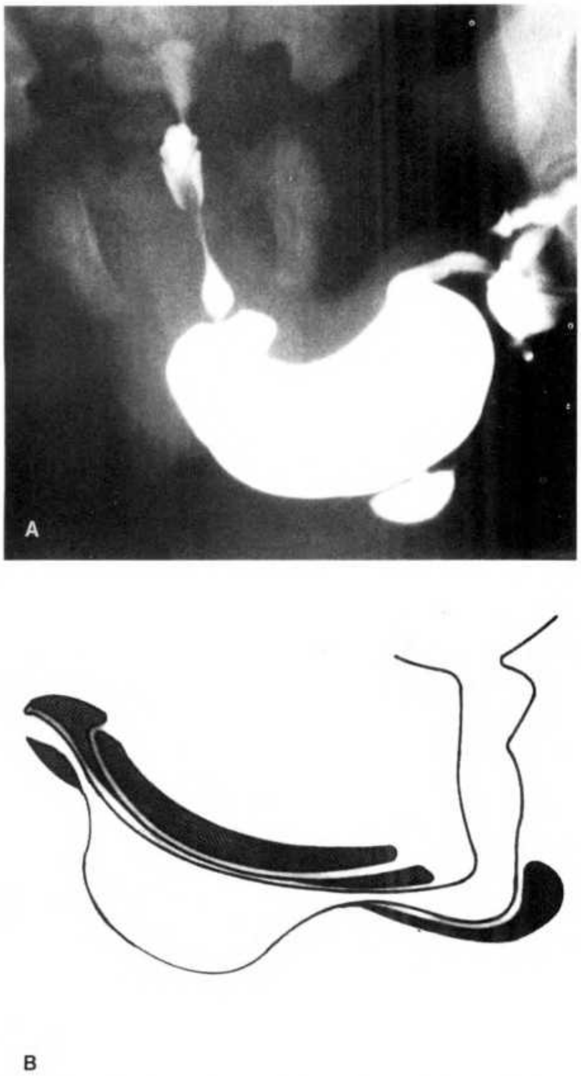

Fig. 3 (A) Pre-operative voiding cystourethrogram with scaphoid expansion of penile urethra. (B) Deficient corpus spongiosum at site of the urethral expansion and bulb.

fusiform or "complete" type is characterised by the additional absence or atresia of the corpora cavernosa. It is associated with a poorer prognosis and a high degree of morbidity and mortality. Megalourethra must be distinguished from urethra diverticula, which are usually located in the proximal penile urethra and cause marked obstruction. Diverticula are caused by a weakness of the urethral wall, which is thinned and dilated at the ventral aspect.

If megalourethra is suspected, a radiographic examination of the upper and lower urinary tracts

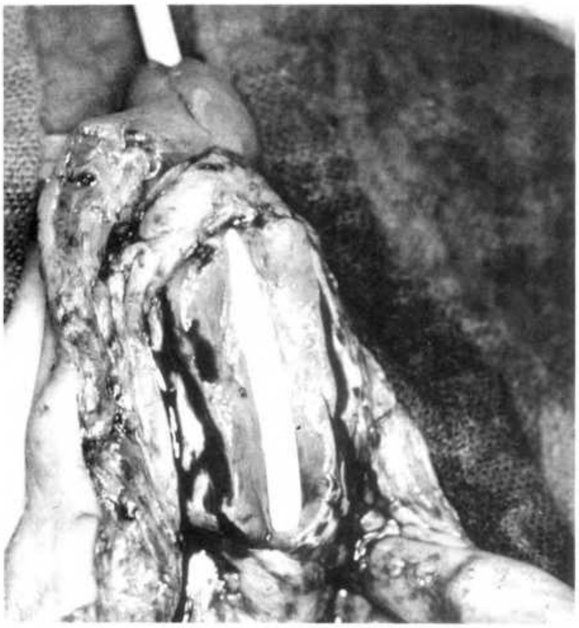

Fig. 4 Intra-operative view of the urethral defect.

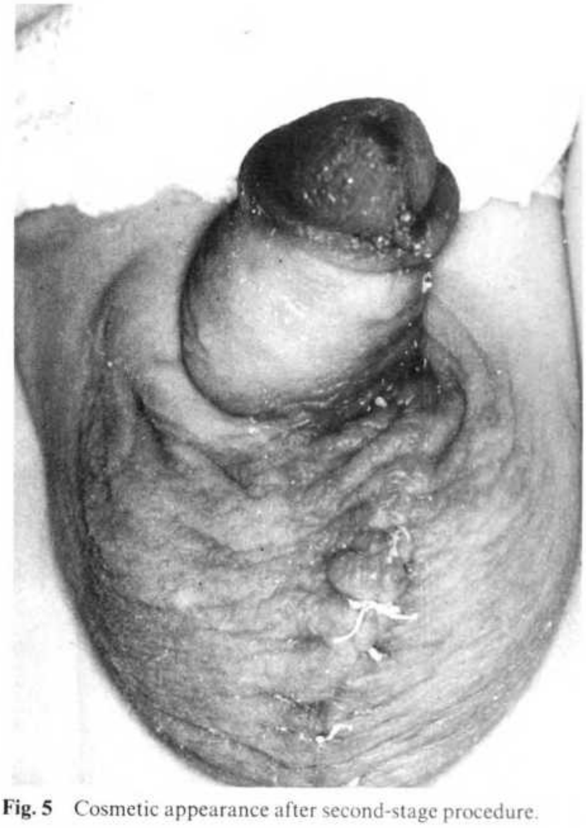

Fig. 5 Cosmetic appearance after second-stage procedure.

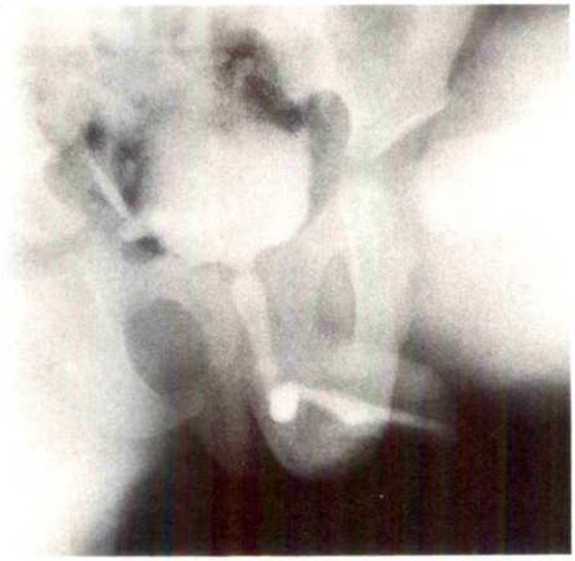

Fig. 6 Post-operative voiding cystourethrogram.

should be performed either by combined urography and voiding cystourethrography or, preferably, by renal sonography and percutaneous bladder puncture with direct application of contrast medium. Retrograde urethrography and endoscopic manipulation should be avoided, because the risk of urinary sepsis is high. Systemic antibiotic medication is advocated. Moreover, it is essential to search for possible accompanying malformations (Nesbitt, 1955; Lindner *et al.*, 1980; Stephens, 1983).

Therapy depends on concomitant pathological findings, but the first step in the management of megalourethra is percutaneous bladder puncture and control of infection. After the diagnosis has been established, surgical correction is performed according to the principles of hypospadias correction. A variety of techniques can produce satisfactory results with regard to both function and cosmetic appearance.

Few cases of 2-stage procedures have been reported so far. This alternative approach involves marsupialisation and subsequent reconstruction of the urethra in a second-stage procedure as shown in our patient.

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Requests for reprints to: A. Reissigl, Department of Urology, University Hospital, Anichstrasse 35, A-6020 Innsbruck, Austria.

Idiopathic Retroperitoneal Fibrosis Treated with Ureterolysis and Wrapping with Expanded Polytetrafluoroethylene Vascular Graft

A. LOH and L. M. SOUTH, *Department of Surgery, Maidstone Hospital, Maidstone*

We present a patient with idiopathic retroperitoneal fibrosis treated with ureterolysis and omental wrapping on one side and expanded PTFE (Goretex) vascular graft wrapping on the other. The latter has been shown to work well in this patient with a 4-year follow-up.

Case Report

A 46-year-old woman presented in January 1986 with cardiac and renal failure. There was no history of analgesic abuse. Biochemistry showed urea 36.8 mmol/l and serum creatinine 972 μmol/l. Hb was 9.9 g/dL and ESR 88 mm/h. She improved after medical treatment. An IVU showed bilateral hydronephrosis with good excretion on the left and marked impairment on the right (Fig.). A barium enema showed complete obstruction at the rectosigmoid junction.

At laparotomy, a mass encasing both ureters and rectum was biopsied, histology of which showed retroperitoneal fibrosis. The left ureter was stented but the right was too obstructed. A colostomy was also performed. Two months later, bilateral ureterolysis was performed. Enough omentum was available for one side; this was used for the left, encasing the rectum as well. On the right, an expanded polytetrafluoroethylene (PTFE) (Goretex) vascular graft was used.

The patient remained well and recent investigations

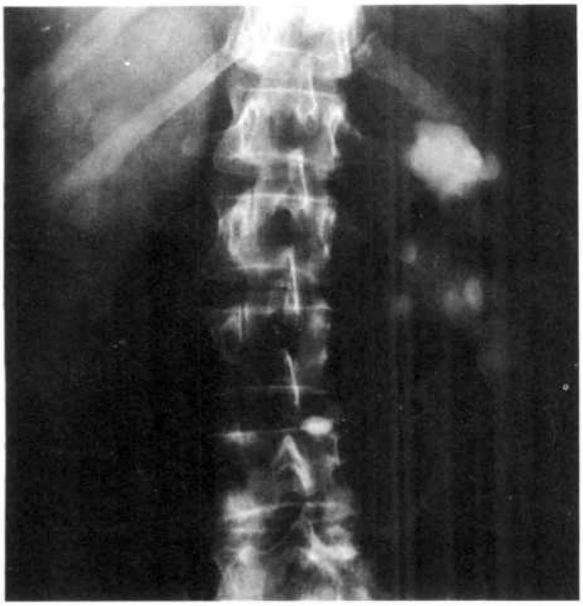

Fig. IVU showing bilateral hydronephrosis with excretion better on the left side.

showed normal urea, creatinine and ESR; a DMSA scan showed the divided function to be left = 26% and right = 74%. Steroids were not used at any time.

Comment

Ureterolysis has been used to treat retroperitoneal fibrosis and results are improved if combined with omental wrapping (Tiptaft *et al.*, 1982) or steroids. Some advocate steroids (Higgins *et al.*, 1988) as a first-line treatment but histological proof is not obtained. A laparotomy was also needed in our patient because of bowel obstruction, which is a rare complication of retroperitoneal fibrosis. Although the follow-up is only 4 years, it does seem that when compared with omental wrapping, the use of an expanded PTFE (Goretex) vascular graft gave better results, especially when it was on the poorer functioning side initially. Further trials are needed to evaluate this technique fully.

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Tiptaft, R. C., Costello, A. J., Paris, A. M. I. *et al.* (1982). The long-term follow-up of idiopathic retroperitoneal fibrosis. *Br. J. Urol.*, **54**, 620–624.

Requests for reprints to: A. Loh, Vascular Unit, Fourth floor, St James' Wing, St George's Hospital, Blackshaw Road, London SW17 0QT.

British Journal of Urology (1991), **68**, 440–442

Points of Technique

Which Ureteric Stent Length?

M. I. WILLS, H. W. GILBERT, D. J. CHADWICK and S. C. W. HARRISON, *Department of Urology, Southmead Hospital, Bristol*

The value of ureteric stenting is well established (Pocock *et al.*, 1986). The correct length of ureteric stent should be used. If the stent is too long it may cause symptoms of trigonal irritation and if it is too short it may retract. At present, the length for each patient is selected by estimation. The possibility of developing a simple formula for more accurate selection of length was investigated.

Technique

Forty adult patients who had undergone ureteric stenting were reviewed. Various factors (sex, height, weight, radiological measurements) were compared with the ideal stent length and the length of the ureter measured on intravenous urography (IVU) was found to have the closest correlation with length ($r=0.68$, $P=0{\cdot}002$). A simple formula (Table) was devised to estimate the ideal stent length from IVU films (Fig.). All films were taken at the standard focus to film distance of 100 cm.

Table Formula

Length of ureter on IVU (cm)	<27	27–29	29–31	33–33	>33
Ideal stent length (cm)	20	22	24	26	28

Thirty patients have had stents inserted, the length of which was determined by this formula, and they have subsequently been assessed. Only 3 sizes of stent were used (20, 22 and 24 cm, Van-Tec). No stent retraction has occurred and symptoms of frequency, dysuria and urgency have been reduced.

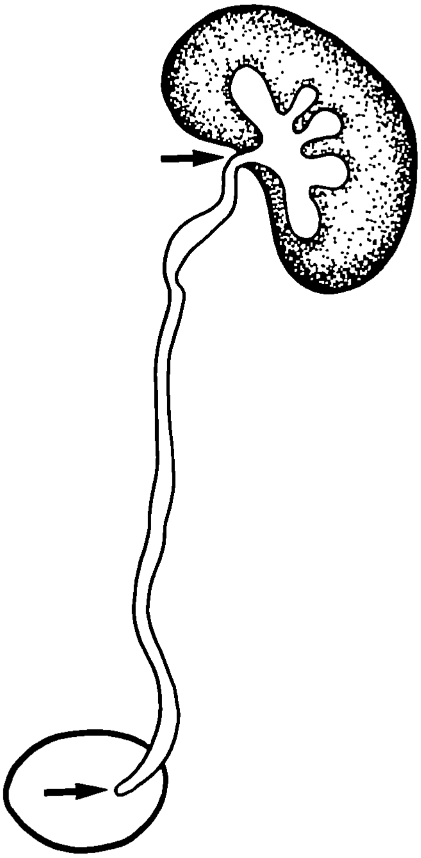

Fig. Length of ureter measured between arrows

Comment

A retrospective review demonstrated a tendency to over-estimate the length of stent required. This may arise from a deliberate attempt to avoid the risk of stent retraction but it causes considerable discomfort to some patients. Using the proposed formula the incidence of such complications can be reduced. In addition, we have found that a very limited range of stent sizes is required. Although the formula is easy to use, in order to apply it a full length IVU film is required.

Reference

Pocock, R. D., Stower, M. J., Ferro, M. A. *et al.* (1986). Double J stents. A review of 1000 patients. *Br J Urol*, **58**, 629–633.

Based on a Poster Demonstration at the 46th Annual Meeting of the British Association of Urological Surgeons in Scarborough, July 1990

Requests for reprints to: M. I Wills, Department of Urology, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB.

New Flexible Cystoscopic Stent Retriever Forceps

S. K. IYER and DOROTHY ALSTON, *Department of Urology, Frimley Park Hospital, Frimley*

Flexible cystoscopy is used more and more frequently for procedures such as removal of ureteric stents, for which various appliances are in common use and some have gained in popularity (Fig. 1). The commonly available biopsy forceps can be used, but with difficulty as the depth of the cups (or the depth of the teeth in the alligator forceps) is such that it is difficult to get a purchase on the stents, especially the larger ones (6 or 7F). The various basket retrievers also have limitations because it is necessary to pass the basket around the end of the stent before the basket can be closed to grasp the stent. This is even more difficult when using a multi-length coiled stent, where there may be problems in locating the end of the stent. Obviously these factors increase the time taken and the discomfort to the patient.

We have recently been using a new type of retrieval forceps of the 'shark tooth type' (a prototype on trial from Keymed). These forceps have 2 short powerful jaws with single opposing pincers on their ends. The length of the jaws is such that they would be useful for grasping larger stents. They can also be applied over any part of the stent visible on flexible cystoscopy (Fig. 2). We have used these forceps on 8 patients while using the Keymed flexible cystoscope and found the accessibility and irrigant flow quite satisfactory. The entire procedure takes less than 5 min with minimum discomfort to the patient. Our impression is that these new retrieval forceps will help the flexible cystoscopist to remove indwelling ureteric stents more easily.

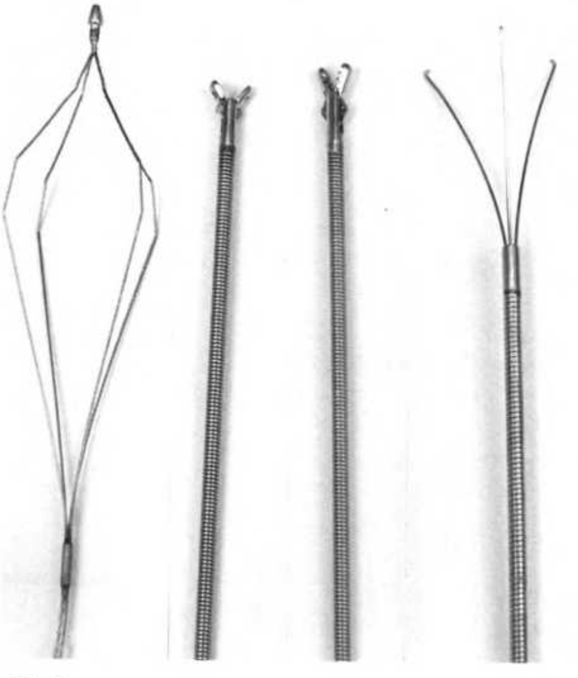

Fig. 1

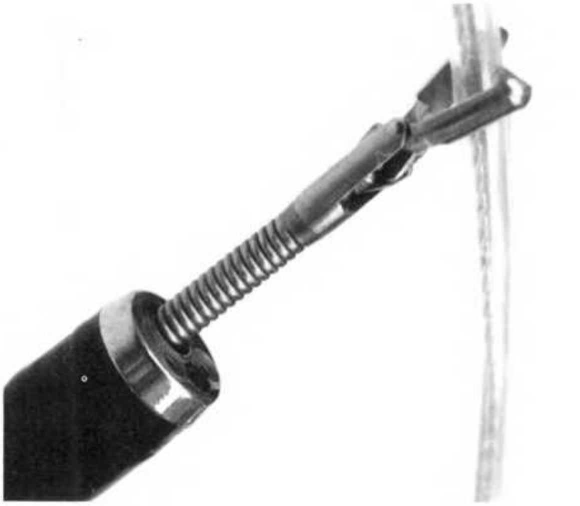

Fig. 2

Acknowledgements

We thank Mr N. H. Hills for permission to use data on some of his patients on whom this device was used. We also thank the Department of Medical Illustrations at St Peter's District General Hospital, Chertsey, for their help.

Requests for reprints to: S. K. Iyer, Urology Department, Chase Farm Hospital, Enfield, EN2 8JL.

Percutaneous Ultrasound-guided Injection of Sodium Morrhuate in the Treatment of Cystic Renal Masses

S. Z. ZOU, W. N. FAN and X. H. HE, *Department of Urology, Nanchong Prefectural Hospital, Sichuan, China*

Between December 1985 and November 1988, 40 patients with a total of 48 cystic renal masses were treated by percutaneous ultrasound-guided injection of sodium morrhuate into the cystic cavity. The group comprised 32 males and 8 females, ranging in age from 29 to 71 years; in 36 cases the cysts were single and in 4 they were multiple.

A 3.5 MHz transducer was used with a needle groove in the middle. A 22 gauge (0.7 mm) or an 18 gauge (1.2 mm) needle was used along the needle groove of the transducer into the core of the cyst. After aspirating the contents of the cyst with a syringe, sodium morrhuate was injected into the cavity. The smallest cyst measured 2.8 × 2.5 × 1.9 cm and the largest 8.4 × 7.8 cm. In the large cysts the volume injected did not exceed 20 ml. Between 12 and 495 ml of liquid were aspirated; this was transparent and yellow in colour.

Follow-up has extended from 4 months to 3 years and the results have been excellent. It was found that 37 cysts had disappeared or diminished by more than a third; 77% were cured by the first procedure but 11 needed a second injection. Complications consisted of pain in 6 cases and temporary microscopic haematuria in 6.

Real time ultrasound scanning permits accurate localisation of the cysts and the manipulations are simple and quickly learned.

Requests for reprints to. S Z. Zou, Department of Urology, Nanchong Prefectural Hospital, Sichuan, China.

Use of Monofilament Nylon for Accurately Localising a Blockage in the Vas Deferens

M. A. LAVELLE, *Department of Surgery, Cuckfield Hospital, Haywards Heath, West Sussex*

In the investigation of azoospermia in the presence of dilated epididymes and testicular biopsies showing normal spermatogenesis, vasograms are useful to show the site of a blockage. However, it is sometimes difficult to match up the X-ray appearances with the anatomical site of the blockage. A technique is described for accurately locating a blockage in the vas deferens at the time of operation.

The patient, A.V., aged 31 years, presented with primary infertility and was found to have azoospermia. Testicular biopsies showed evidence of spermatogenesis and both epididymes were distended. Bilateral vasograms were performed using 5 ml 25% Hypaque injected through a lymphangiogram catheter, as described by Hendry *et al.* (1983). On the right, a patent vas was demonstrated and so an epididymovasostomy was performed. On the left, the vas just above the epididymis was dilated and the vasogram demonstrated a block about 5 cm above the epididymis. A piece of 2/0 monofilament nylon was passed up the vas as far as it would go and the length of nylon inside the vas was marked by clipping a mosquito forceps to the nylon at the point of entry of the nylon into the vas. The nylon was then withdrawn and laid on the skin over the neck of the scrotum. The end of the nylon thus marked the exact point of blockage and a skin incision was made at this point.

The stenosis was excised and a side-to-side vasovasostomy was performed using 6/0 Prolene.

Three months after the operation, the patient's sperm count was 14.5 million/ml and 4 months later the patient's wife conceived. Unfortunately the fetus underwent spontaneous abortion at 8 weeks. At the time of writing the patient's sperm count was 57 million/ml.

Comment

This technique is a useful adjunct to vasography in accurately locating a blockage in the vas deferens. It is a simple technique which enables the surgeon to pinpoint the exact site of the blockage without having to correct for magnification. Vasography is mandatory in all of these cases, to diagnose congenital abnormalities of the seminal vesicles and ejaculatory ducts.

Reference

Hendry, W. F., Parslow, J. M. and Stedronska, J. (1983). Exploratory scrototomy in 168 azoospermic males. *Br. J. Urol.*, **55**, 785–791.

Requests for reprints to: M. A. Lavelle, Department of Surgery, Gatwick Park Hospital, Povey Cross Road, Horley, Surrey RH6 0BB.

British Journal of Urology (1991), 68, 443–445

Book Reviews

Manual of Urologic Surgery. By J. E. Fowler, Jr. Pp. xiii+258. Boston, Toronto, London: Little, Brown and Company. 1990. Price: £60.00.

This book is devoted to operative urology. It is very well illustrated by R.-Z. Li and these figures together with a clear text make for a useful presentation of this subject. The book was first produced by the University of Illinois Office of Publication Services and because it was so successful it has been republished in this current form using the original figures but with an improved text.

Within 250 pages the field of urological surgery is well covered with clear descriptions to match the drawings. While some readers may deplore the use of eponyms—often on the grounds that these persons were not the initiators—they have always remained a useful peg on which to hang particular procedures. Thus it will be disappointing for some British urologists to see the disappearance of the Rutherford Morrison incision, the Hynes-Anderson pyeloplasty, the Cohen ureteric advancement, the Wallace uretero-ileal anastomosis, the Lord's hydrocele operation—to name but a few.

A much more important question is whether or not this text provides the basis of information that a trainee seeks when looking at a book on operative urology: the answer is that it is a very good book but it must be looked at amongst very strong competition and potential purchasers will need to do their own market research before deciding which book they find the most appealing on the subject of operative urology.

Contemporary Management of Urinary Incontinence. Edited by P. H. C. Lim. Pp. xii+144. Singapore, Hong Kong, New Delhi, Auckland, Boston: P G Publishing. 1990. Price: US$35.00.

This small book, though well conceived, falls somewhat short of its aim to give an overview of the contemporary management of urinary incontinence. Whilst aimed at all health care professionals, some will probably be disappointed. Those readers for whom the subject of incontinence is new need a didactic approach and will find confusing the multi-authorship which results in repetition of subject matter and even conflicting information. Those seeking simple guidelines or protocols for dealing with incontinent patients, or who require an update on contemporary thoughts, will not find them in this work. The AMS sphincter, for instance, receives less than 20 lines of coverage in 144 pages and the clam enterocystoplasty is not mentioned once. Readers searching for a reference or authoritative text will, paradoxically, be less disappointed since most of the chapters are, in fact, well referenced.

Although there are chapters that are refreshingly readable and models of originality, it is more difficult to identify a group of potential readers for whom the purchase of this work could be recommended.

Pediatric Urology. Edited by K. W. Ashcraft. Pp. xii+540. Philadelphia, London, Toronto, Montreal, Sydney, Tokyo: Saunders. 1990. Price: £78.50.

Paediatric urology has developed significantly over the past 15 years and this new volume is a valuable addition to the standard texts. Despite the predominance of North American authors the contribution of European surgeons to this specialty is well recognised. The introductory chapters stress the importance of thorough investigation before embarking on surgical treatment and it is enlightening to have a surgeon discuss the management of patients with urinary tract infection. The following 20 chapters deal systematically with the many urological problems encountered in children, including one on the endoscopic treatment of vesicoureteric reflux. Some chapters, however, contain material already featured in other texts, an inevitable consequence when the authors are the acknowledged experts in their fields. Most chapters are easily read with good X-rays, illustrations and line drawings and up-to-date references. Dr Ashcraft has succeeded in his aim of providing an excellent introductory text for all surgeons interested in paediatric urology.

Interstitial Cystitis. Edited by P. M. Hanno, D. R. Staskin, R. J. Krane and A. J. Wein. Pp. xvi+218. London, Berlin, Heidelberg, New York, Paris, Tokyo, Hong Kong: Springer-Verlag. 1990. Price: £55.00.

This is an excellent book on a subject that presents such an enigma to the urologist. The style is easy to read and the sections have been carefully planned with an editorial comment at the end of each one.

Hunner's ulcer may be elusive, but the glomerulations that occur after bladder distension under general anaesthesia are an essential diagnostic feature. Many theories of the pathogenesis are described. Mast cells, expressed as detrusor mastocytosis, are abundant and it is suggested that degranulation of these by substance P or VIP releases histamine, which in turn produces the eosinophilic chemotactic factor. A raised level of eosinophilic cationic protein can be measured in the urine and this has been used to monitor response to treatment. The disruption of the glycosaminoglycan layer of the transitional epithelium is another fascinating concept and possibly this allows toxic substances to penetrate the bladder wall. There is ample food for thought in this compact volume.

Walsh summarises treatment as "an extraordinary gallimaufry of pills, potions and procedures". Certainly a full if not a complete list of therapeutic measures is included, each with a useful explanation of the rationale behind its application. The list of drugs is extensive. Bumpus advocated distension of the bladder under general anaesthesia in 1930 and this has survived the test of time. Jaboulay is credited with the first suggestion to denervate the bladder surgically in 1899. In more recent times, transcutaneous electrical nerve stimulation and the neodymium:YAG laser have been used. For the extreme cases supratrigonal cystectomy and substitution cystoplasty provide a radical approach to the problem.

This book makes a major contribution to any urological library. It carries an extensive list of references and it is hoped that it will initiate many more research studies.

Operative Paediatric Urology. Edited by J. D. Frank and J. H. Johnston. Pp. 246. Edinburgh, London, Melbourne, New York: Churchill Livingstone. 1990. Price: £80.00.

This is not a comprehensive account of urological operations in the child because endoscopic, percutaneous and laparoscopic procedures are excluded. Also excluded are those open procedures, such as operations for urinary stone and renovascular disease, which are technically similar in patients of all ages; nevertheless, many of the operations described, including urinary diversion, pyeloplasty, circumcision and cystoscopy, seem to be in this category.

The preface explains that the book has had a lengthy gestation and in some chapters it shows, for instance, the adverb "recently" is used to describe an event in 1984. The book is liberally and excellently illustrated by one artist, Philip Wilson.

The operations described are those that the editors and the 10 other contributors have found most successful and the book will be of most value to paediatric and urological surgeons who are not regularly engaged in paediatric urology.

Urologic Pathology with Clinical and Radiologic Correlations. Edited by A. Someren. Pp. xi+755. New York: Macmillan. 1990.

The title of this book tells the reader that this is indeed a different type of pathology book. The Editor comments that a multidisciplinary approach to patient care is much talked about but not always achieved. While this book is written primarily for pathologists, the Editor makes a determined and very successful attempt to correlate radiological and clinical findings with pathology. The appeal therefore is to a wide audience of pathologists, radiologists, urologists and nephrologists. The content systematically covers anatomical regions of the urinary tract as well as renal transplantation and the adrenal glands—all in 7 chapters.

To illustrate the layout—using renal oncocytoma as an example—there is a general introduction, clinical presentation, radiologic appearances (with ultrasound and CT), pathologic features (with subheadings of cytopathologic findings, gross findings, histopathologic findings, histogenesis, histochemical, immunohistochemical and electron microscopic findings), natural history and a brief paragraph on therapy. Naturally the emphasis is on the pathology but the correlation with other features is very attractive. The text is well illustrated and the amount of detail from the clinical and therapeutic viewpoint was very readable.

Urologists and nephrologists would do well to have access to this book and pathologists and radiologists will certainly appreciate these successful correlations. An excellent departmental and library book.

Marshall's Physiology of Reproduction. Volume 2. Reproduction in the Male. Fourth edition. Edited by G. E. Lamming. Pp. xvii+966. Edinburgh, London, Melbourne, New York: Churchill Livingstone. 1990. Price: £95.00.

For many years, Marshall's Physiology of Reproduction provided the basis of reference material for reproductive biologists. The fourth edition represents a major revision and extension of the scope of the text. Volume 1, "Reproductive Cycles of Vertebrates", was published in 1984; this volume provides a detailed analysis of the recent research literature on male reproductive physiology, male life cycle and seasonality, the physiology of the testis and accessory sex organs, artificial insemination and preservation of semen. The size of the book is an indication of the vast amount of recent research in the reproductive physiology of vertebrates. A third volume entitled "Pregnancy and Lactation", soon to be published, will be complementary to this volume.

This volume represents the definitive work on the comparative physiology of male reproduction.

Shock Wave Lithotripsy 2. Urinary and Biliary Lithotripsy. Edited by J. E. Lingeman and D. M. Newman. Pp. xiv+462. New York: Plenum Press. 1989. Price: US$89.50.

The Indiana Methodist Hospital's Symposia on Shock Wave Lithotripsy are occasions on which state-of-the-art techniques are reported and the results of basic research are presented. Those who are unable to attend these meetings must scour the urological literature 12 months or more later to read the papers presented at these meetings. Scientific journals are unable to keep pace with the explosion of new technology and research related to stone disease.

Shock Wave Lithotripsy 2 is the answer. The editors have been able to publish the entire proceedings within the same calendar year as the original Symposium in an excellent volume which is full of data relating to all aspects of minimally invasive therapy for urinary and biliary calculi. The presentation of each paper is surprisingly uniform, with an abstract, introduction, materials and methods, results and conclusions appearing in most papers.

The papers are organised into groups on shock wave lithotripsy research, bio-effects of long-term results, biliary lithotripsy, large renal stone management and ureteric stone management and finally a "which" section on treatment results with urological lithotriptors.

The text is clear and typographical errors are few. This book is to be recommended to all clinicians involved in stone treatment for detailed consumption or simply for obtaining an up-to-date overview. At a price under £50 this book is excellent value and should appear in the library of all Stone Centres.

The editors hope that "publication of this material will be a real benefit to those interested in the various aspects of treatment with shock wave lithotripsy". Their hope is fulfilled, since there is much to inform clinicians and basic scientists working in the field of lithotripsy and related treatments.

Refreshingly, there is little of the "me too" syndrome; but a caveat: the articles have not been peer reviewed and although many of the authors are established experts in their field we are not privy to the discussion which centred around the presentations and the reader would do well to keep a supply of salt on hand.

Dry All Night: The Picture Book Technique that Stops Bedwetting. By Alison Mack. Pp. x+176. Boston, Toronto, London: Little, Brown and Company. 1989. Price: US$17.95.

This is a new book which comes from the author of "Toilet Learning", with the picture book technique for children and parents which has been popular, particularly in the United States, in helping children to become toilet trained. This new book tackles the more psychological aspect and provides a simple, informative, step-by-step approach to parents. Half of the book is set aside as a colourful story for children to read themselves. Although this requires some reading stamina, it is an imaginative tale which promises to teach the children the steps they can take to help themselves to be dry at night.

Anyone who has a child who is bedwetting would be delighted to see such a refreshing approach which really helps the child to conquer the problem by his/her own efforts

British Journal of Urology (1991), 68, 446

Notices

British Association of Urological Surgeons

President: R. E. Williams, MD, ChM, FRCS, FRCSE

Annual Meeting: Bournemouth. 21–26 June 1992

Abstracts of contributions to be considered as either papers, posters or videos by the Programme Sub-Committee of Council should be submitted on the special forms, which will be available from the BAUS Secretariat in October 1991. Completed forms, which should state clearly whether the submission is a paper, a poster or a video, must be returned to the Honorary Secretary by Friday, 10th January 1992.

Abstracts not on the special forms will NOT be considered.

All correspondence to: R. J. Morgan, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

The Surgitek Prize

The Prize consists of a fully sponsored visit to the American Urological Association Annual Five-day Meeting, together with a tour of Surgitek's manufacturing facility in Racine, Wisconsin. It is open to trainees in urology and consultants who are within 5 years of first appointment. Entrants should submit a written paper, which may be on any subject, but must be unpublished, and must not have been submitted previously for the Surgitek Prize, or other prizes. The winning entry will be the one which is considered to be "The most significant contribution to urology".

Entries will be judged by three members of BAUS Council nominated at the October meeting of Council. Papers should be submitted in triplicate to the Honorary Secretary by 1 January each year.

Surgery in the Third World

Sir Ian Todd, past President RCSEng, is anxious to build up a list of surgeons in all specialties from the United Kingdom and Northern Ireland (active or recently retired consultant, or higher surgical trainee) who would like to spend some time working and teaching in a third world country.

In most cases accommodation and subsistence are provided and in some air fares also. Periods abroad vary from 1 month upwards but 3 to 6 months are usually preferred.

Please write to Sir Ian Todd, KBE, FRCS, care of the Overseas Doctors Training Scheme Office at the Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN.

Notices

Bard Award

This award, made possible by the generosity of C. R. Bard International Limited, was made for the first time at the Annual Meeting in Bristol in 1979. The award will consist of the sum of £1500 and the Bard Silver Medal. The award will be given for the best essay submitted specifically for consideration for the award by members of the Association (non-members must be sponsored by a Full Member).

Essays should be based on original work on any topic connected with urological surgery, either clinical or experimental. The essay should include a review of the literature and the clinical implications of the work performed. A panel of three adjudicators will be nominated at the February meeting of Council each year. Submissions for the award should be made in triplicate by 1 March to the Honorary Secretary. The winning essay will be read during the Annual Meeting and should not exceed 20 minutes in duration.

British Journal of Urology (1991), **68**, 447–448

Diary

1991	
October 3–5	Prostate Cancer and Urothelial Cancer; Controversies in Diagnosis and Treatment, Orlando, Florida. Contact: Imedex U.S.A. 1060 Cambridge Square, Suite D, Alpharetta, Georgia, U.S.A.
October 3–5	Annual Meeting of Swiss Society of Urology, Geneva, Switzerland. Contact: Prof. Dr D. Hauri, Urologische Klinik, Universitätsspital, CH-8091 Zürich, Switzerland.
October 4–5	Autumn Meeting, Royal Surrey County Hospital, Guildford. Contact: BAUS Office.
October 9–12	1st International Congress, Dutch Urological Association (NVU), Rotterdam. Contact: NVU/PACIOU Congress Secretariat, Department of Urology, Erasmus University Rotterdam/Academic Hospital Dijkzigt, P.O. Box 1738, 3000 DR Rotterdam. The Netherlands.
October 10–12	International Continence Society, 21st Annual Meeting, Hannover. Contact: Guus Kramer, Chairman ICS, Department of Urology, Hannover Medical School, P.O. Box 610180, 3000 Hannover 61, Germany.
October 18–19	Surgical Treatment of Prostatic Cancer: Comparison of Techniques. Milan, Italy. Contact: Dr F. Gaboardi, Divisione di Urologia, Ospedale Fatebenefratelli ed Oftalmico, C.so Porta Nuova 23, 20121 Milan, Italy. Tel. 0039-2-636443.
October 19–20	Complications in Urology, New York, USA. Contact: Ann J. Boehme, Associate Director for Continuing Education, Long Island Jewish Medical Center, New Hyde Park, New York 11042, USA.
October 20–November 4	Royal College of Surgeons of England Joint Meetings in Pakistan and India. Contact: Craig Duncan, Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London, WC2A 3PN.
November 15	Paediatric into Adult Urology. Birmingham. Contact: Miss J. Snowden, Department of Urology, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH. Tel: 021 472 1311, Ext. 3287.
November 15–16	Third Biennial Asia-Pacific Meeting on Impotence, Taipei, Taiwan, R.O.C. Contact: Third Biennial Asia-Pacific Meeting on Impotence, c/o Taiwan Conference Management Co. Ltd, P.O. Box 68–439, 6F–3, 102 Chung Shan N. Road, Sec. 2, Taipei, Taiwan, R.O.C.
November 21	Controversies in the Management of Prostatic Cancer, St Bartholomew's Hospital. Contact: Dr A. Jelliffe, NETRHA, 40 Eastbourne Terrace, London, W2 3QR. Tel: 071 262 8011.
November 22–23	International Pelviureteric Junction Obstruction Symposium, Stratford-on-Avon. Contact: Mr P. Shridhar, Department of Urology, George Eliot Hospital, Nuneaton CV10 7DJ.

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January 10	Final date for submission of abstracts for the 1992 BAUS Annual Meeting.
March 8–13	19th Biennial Congress of the Urological Association of South Africa, Sun City, South Africa. Contact: Dr I. Lissoos, 1 Esselen Towers, Esselen Street, Hillbrow, 2001, South Africa.
March 19–21	Eleventh International Symposium of Operative Andrology. Istanbul, Turkey. Contact: Dr A. Kelâmi, Brahmsstrasse 32, D-1000 Berlin 45, Germany.
March 19–21	Searching for Prostatic Carcinoma: the Problem of Screening and Early Detection. Munich, Germany. Contact: D. Née, Secretariat, Department of Urology Krankenhaus der Barmherzigen Brüder, Romanstr. 93, W-8000 Munich 19, Germany. Tel: 89/1793-252 or 89/17 56 61. FAX: 89/1782653.
March 26–27	Eighth Annual Symposium on Progress in Paediatric Surgery, Oviedo, Spain. Contact: Dr J. L. Teixidor de Otto, Servicio de Cirugía Pediátrica, Hospital Central de Asturias, Centro Universitario, E-33006 Oviedo, Spain.
April 9–11	6th International Urological Symposium. Girne, North Cyprus. Contact: Dr A. Kelâmi, Brahmsstrasse 32, D-1000 Berlin 45, Germany.
May 6–8	8th International Symposium on Radionuclides in Nephrourology, The Grosvenor Hotel, Chester, England. Contact: Mr P H O'Reilly, Department of Urology, Stepping Hill Hospital, Stockport, SK2 7JE.
May 10–14	American Urological Association, Washington Convention Centre, Grand Hyatt, Washington DC.
May 24–28	Inaugural Meeting of Pan African Urological Surgeons' Association, Harare, Zimbabwe. Contact: Mr A. P. Danso, Department of Surgery, University of Zimbabwe Medical School, P.O. Box A 178, Avondale, Harare, Zimbabwe.
June 4–6	Fourth International Meeting of Andrology, Como, Italy. "Treating Male Infertility: New Possibilities". Contact: Dr G. M. Colpi, II Divisione di Chirurgia, Centro di Andrologia e Infertilita, Ospedale "VALDUCE", Via Dante 11, I-22100 Como, Italy.
June 10–12	Continent Urinary Reconstruction. First International Meeting. Lund, Sweden. Contact: Dr Wiking Månsson, Department of Urology, University Hospital, S-22185 Lund, Sweden.
June 22–25	Canadian Urological Association Annual Meeting, Winnipeg. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.
July 22–25	European Association of Urology, 10th Congress, Genoa. Contact: Conference Secretariat, Top Congress—P.R., Piazza Galeazzo Alessi 2/1, 16128 Genoa, Italy.
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August 24–27	Third European Symposium on Uroradiology. Herlev, Denmark. Contact Dr H. S. Thomsen, Department of Diagnostic Radiology 54E2, Herlev Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark.

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Wright, F. S. and Howards, S. S. (1981) Obstructive injury In *The Kidney*, ed Bremner, B M. and Rector, F C. Second edition Volume II Chapter 38, pp 2009–2044 Philadelphia Saunders

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REVIEW

Informed Consent—Issues for the 1990s

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It is my contention that enough words have already been written on the core matters of informed consent and what is now needed is for the medical mind to focus on some residual but key issues. As with other features of our professional world unless we do so, others are likely to take them over from us, imposing a new interpretation which may ignore or even actively oppose a long tradition of medical understanding and a hard won relationship of trust. I wish to tackle 3 matters: the meaning of "informed", randomisation in clinical trials, and the use of volunteers in research.

Informed Consent

It has long been conceded that "the term 'informed consent' is a relative one" (Duncan *et al.*, 1981) and in recent years this has been upheld in the law courts. Relativity is composed of a number of things. First, none of us knows everything about any condition we treat, though in some circumstances we are better informed than others. Second, and partly as a extension of inadequate knowledge, we cannot invent the future. Third, what predictive power we have is based on probabilities which, as every modern school boy now knows, are numerical values calculated from "runs" of events and cannot by their nature tell us what is going to happen to an individual. The mind has a way of coping with this difference between group and singularity by effectively in behavioural terms ignoring very small probabilities. If we really considered these we would never cross the street, undertake to travel by air or have a general anaesthetic. Just where we stop ignoring small measures of risk has been the subject of some rather inconclusive research. Fourth, what understanding we have of disease and therapy is couched in a professional vocabulary (I prefer that word to the commonly used "jargon" which more often than not carries the overtone of deliberate intent to confuse). Understanding what is behind the use of a word or phrase comes only from long familiarity with the context and the purpose to which the expressions are put in practice. Instant grasp of the new is impossible. Witness for example the bizarre attempts by lay people to locate their internal organs (Pearson and Dudley, 1982), never mind to understand function and the disease processes that might afflict them. I am struck repeatedly by how often well-meaning groups of lay people abuse professional vocabularies by the "naming of parts" which appears to give authority but in fact only expresses semantic ignorance; having a word at one's disposal does not necessarily mean that you have grasped its specific intent. Even as a professional it is easy to fall into the trap that, because a patient does not question your use of a word, she really has its meaning clear in her mind.

To make such potentially derogatory remarks is not to dispute an ability to acquire (in the best sense of that word) the rudiments of a professional vocabulary even if one is not a paid up member of the group. The Ileostomy Association and the Kidney Patients Association are cases in point; both are long-standing aggregations of patients who have, through judicious advice and their own experiences, conquered and come to terms with the proper meaning of the words they use. However, they are the exceptions rather than the rule and pressure groups formed to uphold, amongst other things, the patient's right to know are often plagued by the spurious nature of their understanding. The relative nature of "informed" is not often appreciated by those who have as an axiomatic starting point the belief that, as one of Shaw's characters in the Doctor's Dilemma put it, "professions are conspiracies against the laity". Not much can be

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done to counter this blanket assumption of secrecy and self-protection, particularly in our media-driven society, though most would concede that our stance in the matter has, with a few notable exceptions, been remarkably flaccid.

However, my concern here is with what we can do about dialogue with the individual patient whose agreement to a diagnostic or therapeutic procedure is being sought. My view is that it would be sad if we went down the pathway of more and more detailed explanation of possible though potential hazards of low probability. This seems to have been what has happened in North America as a consequence of the accusatory retrospective finger of the law waggling as its owner says "why did you not inform my client of this or that occurrence?" which we know to be a well nigh fortuitous hazard. Detailed explanations to counter such a legal approach must inevitably be biassed towards the "downside", which is unfair to the doctor-patient relationship. Doubts aroused cannot always be formally countered by the prospect of benefits which will accrue, however apparent these may be to the surgeon. It is true that self-help groups can assist her by pooling experience of operations and their "upside" but for the most part this benefit has only been exploited in special circumstances. There is also the risk that associations whose role can be to explain on a lay person basis what advantages can be gained will degenerate into doom and gloom merchants as they meet to share difficulties. Such was certainly true of the early days of the Ileostomy Association.

I believe that in seeking consent we must try to inculcate more formally into our patients the concept of life as a risk-taking exercise in which both we and they are incompletely informed. This interacts with the existentialist paradox that patients, for their emotional security, want us as their advisors to be assured and complete in our knowledge, while at the same time they reserve the right to deny us this quality if things go wrong. I do consider that most patients understand risk as a common or garden factor of life, though their immediate and often unrestrained reaction to any unfavourable results of risk taking varies with the setting—as we have seen from the recent spate of civilian disasters. We have been slow to realise that fatalism is no longer the established order of the day. As I mentioned, there is some difficulty in deciding at what level of perceived risk the odds become important in decision making by the patient; perhaps a figure cannot be put on this—so varied are the contexts. it would be too sweeping a generalisation to say that single figure values for probabilities of most medical risks seem to hold little fear but it is a premise worth thinking about. In conclusion to this matter I feel that the most important message to get across is the incompleteness of information on both sides; I realise nevertheless that as long as the legal profession is involved in debating liability for error or for untoward events we are unlikely to have a truly informed debate on how much in quality and quantity we must tell our patients in the interests both of them and ourselves.

Clinical Trials and Randomisation

The issue of informed consent has found a focus not only in straightforward management but also in the more tortuous pathways of experiment. The common one is the prospective randomised controlled clinical trial (PRCCT) where random allocation to one or other arm of treatment (one arm sometimes being *no* treatment) often seems to the patient to be a denial of the role she has cast the doctor to play. I share this view because it is difficult—may be impossible—for the patient to believe in the "null hypothesis" that the doctor really does not know which treatment is better. To do this flies in the face of the reason she has taken his medical advice. It is further compounded by her not unreasonable inability to make the distinction between herself as an individual sufferer and what may be advantageous to the next hundred or so patients with a similar problem. Such is a contrast we all face in everyday life between self-interest and the Benthamite principle of the "greatest happiness for the greatest number". Furthermore I would like to suggest that to adopt the null hypothesis and attempt to disprove it—though admirable in scientific terms (and also the foundation of the classical statitstical analysis used in controlled trials)—is not a natural thing to do. Though, as I have already indicated, generalisation and prediction therefrom are risky, it is how we conduct our lives. We do use, and as humans could not survive without, prior knowledge as distinct from approaching everything with an open mind. Often ineffective treatment rests not on the absence of some prior knowledge of this kind but on our refusal to recognise that it extists as a potential determinant of what we should do. The null hypothesis can sometimes be an active discouragement to careful thinking. Few clinical advances, as distinct from checks on the applicability of therapy, have come from taking the null hypothesis and conducting a "blind" trial which the investigators deliberately eschew any feeling that one method of management is better than another. It does, however, remain true that controlled trials can rein in exuberant over-exploitation of ill-defined hypotheses not based on rational knowledge or hard thinking. Here may lie their best use.

The ethical problem of obtaining informed consent to randomisation is not solved by pejorative phrases such as "it is unethical not to do a trial when we are uncertain about the best therapy" nor is it alleviated by the need to ensure statistical significance for our results so that they can gain publication in a reputable journal. Fortunately the tide seems to have turned against randomised trials which do not first explore very deeply the need for a trial at all (true uncertainty about outcomes which we have established as a rare event (Byar *et al.*, 1990)) and then the feasibility of asking either patient or doctor if randomisation is possible or desirable. Recent unsuccessful attempts to recruit patients into trials of mastectomy versus local excision for the regional management of breast cancer or for open versus laparoscopic cholecystectomy have shown that neither participant is happy with informed consent to randomisation in its present form. The severe strains such trials impose on both parties in explaining and obtaining informed consent—strains which have been less well articulated from the professional side than they have been by patients—testify to the real problem of applying scientific standards to everyday life. Though in theory scientific rigour dictates the need for controlled trials with randomisation, these were originally conceived when the profession had a more patrician approach to patients; now such trials look increasingly artificial abstractions from the real world and their days may well be numbered.

Time was when, as an imitative patrician myself, I was prepared to withhold obtaining as fully informed consent as I could manage in circumstances where I felt that, on the one hand, confronting the patient with her mortality was unfair and, on the other hand, that the additional treatment I was proposing she should be randomised either to receive or not was harmless and might do good. Now I know that it is never true to say that one can assume lack of harm. However, I still believe that, in the philosophical sense and perhaps because of the cultural legacy from Plato's closed society (Popper, 1945) in which I was raised, one may withhold information from a patient if it is felt that it may do them a disservice. But it has to be admitted that it is increasingly not possible to do so in the social context where a failure to inform has been elevated to the status of a professional sin. Again we are dealing with a manifestation of the conspiracy theory of the medical profession and, in consequence, of the lack of trust between doctor and patient. This important social issue, though outside my remit, is one that is crying out for debate as distinct from polemic.

Volunteers in Research

Lastly I want to draw attention to yet another barrier that has arisen in the path of obtaining informed consent for clinical experiments. I have already implied that the old doctrine of *primum non nocere* is also relative—any interaction between individuals or groups, however ostensibly beneficial, can have its risks. It is becoming increasingly apparent that this can be unwittingly true for human experiment. When the post war British atom bomb tests were carried out no one felt that "volunteers" exposed to the blast were likely to sustain harm—the molecular mechanisms of radiation damage were still poorly understood and we were unaware that there was no innocuous subthreshold dose. Now better understanding and superior measuring devices in the physical and epidemiological areas call this view in question and retrospectively undermine the validity of any consent obtained. What causes more concern is the increasing sensitivity of our ability to measure epiphenomena—that is changes which are part of the effect of what we do but are not contained in our hypothesis. A crude example is thalidomide, where the hope was to relieve pregnancy symptoms but the side effects were grotesque. More subtly we are now able to measure aspects of brain function, of genetic modification and of mediator activity which seem not currently to have any great significance but which may, 20 or 30 years hence, prove to have been the initial indications of some undesirable effect. Further, we do not have the background information to sift such potentially man-induced changes from the ordinary hazards of exposure to the world which go unrecognised or unquantified until time and Nemesis supervene. In the context of informed consent, if we want to try something new or different either as an experiment in humans or even as potential therapy, we risk being ever more inhibited from action because in answer to the question "may it cause harm?" we shall have to say: "first there are measurable effects but we do not know what they mean and in any case the definition of harm is difficult and arbitrary"; and "second we cannot say *no* with a measurable degree of certainty". How to deal with this increasing problem is only just beginning to trouble some of us, though it will not I believe be long before it comes to occupy centre stage.

Urologists are often (unfairly) characterised as down to earth pragmatists untroubled by philosophical concerns. However, as they increasingly use physiological investigation and new operative and non-operative techniques they must tackle the issues of the day along with the rest of us. It has recently been rather assumed that "informed consent" is no longer such an issue. I hope that I have shown that this is not the case and that, for the foreseeable future, we face dilemmas and doubts.

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Does Further Extracorporeal Lithotripsy Promote Clearance of Small Residual Fragments?

N. J. PARR, A. W. S. RITCHIE, G. SMITH, S. A. MOUSSA and D. A. TOLLEY

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Summary—Small persistent fragments ($\leqslant$4 mm) following extracorporeal shock wave lithotripsy have been termed clinically insignificant residual fragments (CIRF), but their presence may be associated with an increased rate of development of recurrent symtomatic renal calculi. We have adopted a policy of further extracorporeal piezoelectric shock wave lithotripsy (EPL) for patients with CIRF in an attempt to promote complete clearance.

A series of 22 patients with a mean initial stone burden of 16 mm (range 7–48) developed CIRF after a median of 2 EPL treatment sessions (range 1–9). CIRF were in the lower calices (n = 20), middle calices (n = 1) and upper calices (n = 1). These calices were normal (n = 6), slightly dilated (n = 9), moderately dilated (n = 2) or grossly dilated (n = 5). After 6 to 14 months, patients underwent a further session of EPL. One month later, 3 patients with normal calices had become stone-free, 1 patient with normal calices and 3 with slightly dilated calices showed a considerable reduction in CIRF, but all other patients showed no change.

When CIRF form in normal calices a further session of EPL may promote clearance. However, when calices containing CIRF are significantly dilated, further EPL is of no value.

Extracorporeal shock wave lithotripsy (ESWL) is now widely used in the treatment of renal calculi. The majority of patients become completely stone-free within a few months of treatment, providing that fragmentation of the calculus has been satisfactory. However, a few patients are left with small residual fragments which fail to clear from the collecting system despite prolonged follow-up.

Small residual fragments ($\leqslant$4 mm) have been termed clinically insignificant residual fragments (CIRF). Nevertheless, evidence suggests that patients with CIRF develop recurrent symtomatic renal calculi at more than twice the rate of those who become completely stone-free after lithotripsy (Newman *et al.*, 1988). Since extracorporeal piezoelectric shock wave lithotripsy (EPL) requires neither anaesthesia nor analgesia (Marberger *et al.*, 1989; Neerhut *et al.*, 1989), we have offered patients with CIRF a further session of EPL in an attempt to promote complete stone clearance.

Patients and methods

A series of 22 patients with CIRF underwent a further treatment session of EPL. Their mean age was 50 years (range 19–78). The mean time from their last treatment session to this additional session was 8.5 months (range 6–14). The characteristics of their initial stone(s) and the number of previous sessions of EPL are shown in Table 1.

All EPL was carried out on a Wolf 2300 Piezolith. One month after the additional session of EPL each patient underwent a KUB (kidney, ureter and bladder) radiograph and the response of the CIRF to treatment was assessed.

Results

The site of the CIRF, caliceal anatomy, the number of shock waves delivered and the outcome 1 month after treatment are shown in Table 2. The calices in which the CIRF were lying were judged, from a pre-treatment intravenous urogram, to be normal (n = 6), slightly dilated (n = 9), moderately dilated

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Table 1 Site and Characteristics of Original Stone(s) and Number of EPL Sessions to Produce the CIRF

Site	*Single/ Multiple*	*Stone burden (mm)*	*Previous EPL Sessions*
LC	S	8	1
LC	M	18	1
LC	M	26	4
UC	S	29	9
LC	M	24	5
LC	S	9	3
MC	S	14	4
LC	S	10	2
P	S	15	1
LC	S	7	1
PUJ	S	11	1
LC	M	12	1
LC	S	12	3
LC	S	8	4
P	S	28	9
LC	S	14	1
LC	M	10	3
P, LC	M	48	6
LC	S	16	2
LC	S	7	2
LC	S	11	2
LC	S	16	1

LC = Lower calix. MC = Middle calix. UC = Upper calix P = Renal pelvis. PUJ = Pelviureteric junction. S = Single stone. M = Multiple stones.

(n = 2) or grossly dilated (n = 5). Three patients with normal calices became stone-free at 1 month. Three patients with slightly dilated calices and 1 with normal calices showed a considerable reduction in CIRF. One of these 4 later underwent another session of EPL and became completely stone-free. All other patients showed no change in their CIRF.

Discussion

It would be ideal if all patients were rendered completely stone-free by ESWL. However, as experience with this technique increases, it is becoming apparent that a proportion of patients will fail to clear all fragments despite adequate disintegration.

When fragments consist of struvite, and particularly in the presence of infection, experience from both open (Singh *et al.*, 1975) and percutaneous nephrolithotomy (Patterson *et al.*, 1987) suggests that there will be a high rate of recurrent stone formation. When struvite fragments persist in a dependent calix after ESWL, a case can be made for percutaneous extraction in order to break a vicious circle of new stone growth and infection.

In the absence of these 2 factors, management is less clear. CIRF have been defined as fragments remaining in the kidney that are small ($\leqslant$4 mm), asymptomatic, not composed of struvite, and associated with sterile urine (Lingeman *et al.*, 1989). Nevertheless, patients with CIRF after ESWL developed new stones 1 year after treatment in 21.6% of cases, compared with 8.4% in those who became stone-free after ESWL (Newman *et al.*, 1988). It is suggested that these fragments provide a nidus upon which new crystalline material may be deposited. It is noteworthy that the rate of new stone growth for patients who became stone-free is similar to the annual incidence of new stone formation in untreated patients with a history of calcium nephrolithiasis (Marshall *et al.*, 1975).

In our experience, fragments often continue to clear for 2 to 3 months after EPL, and occasionally for up to 6 months. Fragments which remain beyond this time are unlikely to pass spontaneously. Therefore, when adopting a policy of further EPL to patients with CIRF, we decided to wait at least 6 months from the last session before offering further treatment. Although the numbers treated in

Table 2 Site of CIRF, Caliceal Anatomy, Number of Shocks Delivered to CIRF and Assessment of Outcome 1 Month Later

Site	*Anatomy*	*No. of Shocks*	*Outcome*
LC	+++	2500	No change
LC	+++	3000	No change
LC	+++	3500	No change
LC	+++	4000	No change
UC	+++	3600	No change
LC	++	3000	No change
LC	++	2000	No change
LC	+	2000	No change
LC	+	2000	No change
LC	+	2500	No change
LC	+	2500	No change
MC	+	2600	No change
LC	+	2500	No change
LC	+	2000	Reduced
LC	+	3000	Reduced
LC	+	4000	Reduced
LC	–	2000	No change
LC	–	2000	No change
LC	–	2000	Reduced
LC	–	4000	Stone-free
LC	–	2000	Stone-free
LC	–	1500	Stone-free

LC = Lower calix MC = Middle calix. UC = Upper calix +++ = Grossly dilated calix. ++ = Moderately dilated calix. + = Slightly dilated calix. – = Normal calix, this way were small, it soon became obvious that when CIRF form in normal calices, further EPL may be worthwhile. However, when the calices containing CIRF are significantly dilated, further EPL is of no value. For these patients a conservative policy would seem sensible. Should symptomatic stones recur, percutaneous extraction is probably preferable to further EPL. In the small group of patients with rapidly recurring stones in grossly dilated lower pole calices, partial nephrectomy remains an option (Timoney *et al.*, 1988), particularly when the patient is young and fit.

In conclusion, these results emphasise the importance of studying the intravenous urogram when following up patients with residual fragments after ESWL and help to clarify the worthwhile endpoint of this form of treatment.

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Idiopathic Kidney Stone Formation—Where and Why?

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Summary—An attempt was made to analyse where and why stone formation in the kidney starts. For this purpose specific electrical conductivity (SEC) of the serum and urine of the same individual in 50 cases of stone formers (Group I) and 50 controls (Group II) was measured. The mean serum value of SEC at 37°C and 50 Hz in μmho/cm of Group I was 1.23×10^4, while that of Group II was 1.20×10^4. This was not statistically significant. However, urinary SEC values did differ significantly between the 2 groups. An analysis of observations reveals that in the case of stone formers there is a fault in the solute transfer system in the kidney at the membrane level (urothelium).

The specific electrical conductivity of urine in stone formers is low compared with that of non-stone formers (Chhabra and Manocha, 1985; Manocha *et al.*, 1987). The dielectric constant (combination of charges) of stone formers' urine is also considerably decreased; however, the total amount of urinary solute per unit volume is the same in both, indicating that urinary solute in stone formers is in a complexed form, but present as free charges in non-stone formers (Manocha *et al.*, 1987). Why and where this decrease in SEC and dielectric constant occurs during the transit of fluid in the nephron have not yet been determined.

The transfer of solute across the tubular membrane takes place via various interdependent mechanisms. Important amongst these is the electrostatic potential gradient. The potential due to charge separation across the membrane can be expressed by the equation

$$\psi = \frac{\sigma d}{E_m E_0} \qquad (1)$$

Where σ is the charge density, d the membrane thickness, E_m the dielectric constant of the membrane and E_0 the permitivity *in vacuo* (John, 1980). There are 3 compartments where the changes referred to above could take place: (i) the blood compartment, (ii) across the membrane, (iii) in the urine.

Since the solute and solvent in the 2 groups are quantitatively similar (Manocha *et al.*, 1987) the changes are unlikely to be initiated in the luminal urine; they must, therefore, take place either in the blood compartment or across the membrane.

Patients and Methods

The study was carried out in 100 adult subjects of both sexes divided into 2 groups. There were 50 idiopathic renal stone formers (Group I). The control group comprised 50 normal healthy adults with no radiological evidence of calculus disease (Group II). Both groups were evenly matched for sex and age. Most of the subjects were vegetarians. All were instructed not to eat or drink after 10 p.m. and alcohol was not permitted on the night before the examination.

A midstream and fasting morning sample of urine was collected in specially prepared, dry, autoclaved bottles which had been cleaned and washed with double distilled, non-ionised water. A blood sample was obtained after collecting the urine sample, but before breakfast; 10 to 12 ml of venous blood were withdrawn and allowed to clot over 1 h; the blood was then centrifuged for 15 min for separation of serum. The SEC was performed according to the technique previously described for biological fluids (Chhabra and Manocha, 1985;

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Manocha *et al.*, 1987). All of the analyses were carried out at 37°C and 50 Hz. The apparatus used was a conductivity meter, based on the principle of the Wheatstone Bridge, type 305 (manually operated) supplied by M/s Systronics, Ahmedabad (India). The apparatus was tested intermittently for accuracy and sensitivity by the known values of SEC of potassium chloride solution. The urine samples of the 2 groups were tested under identical physical conditions.

Results

The mean ± SD values for the SEC of urine and serum expressed as µmho/cm in the 2 groups are shown in the Table. The SEC value of the urine in the stone formers (mean ± SD: $1.05 \times 10^4 \pm 0.28 \times 10^4$ µmho/cm) was significantly less ($P<0.001$) than that of the non-stone formers (mean ± SD: $2.29 \times 10^4 \pm 0.51 \times 10^4$ µmho/cm). However, there was no statistical difference in the SEC value of the serum between the stone formers and non-stone formers.

Discussion

This study has shown that the SEC values of the urine of stone formers differ significantly from the values in non-stone formers, as was observed in our earlier studies (Chhabra and Manocha, 1985; Manocha *et al.*, 1987). The serum SEC values in both the stone formers and the control group were the same and consistent with the levels reported by Sunderman (1945) and Singla (1983). The mean urinary SEC value in non-stone formers was almost double that of the stone formers as well as double the value of the serum SEC values for both groups. The urine SEC value in the stone formers was equal to the serum SEC value.

Thus, re-writing Eqn (1) with subscripts "nsf" for non-stone formers, and "sf" for stone formers, the following equations can be derived:

$$\psi_{\mathrm{nsf}} = \frac{\sigma_{\mathrm{nsf}}\, d_{\mathrm{nsf}}}{(E_{\mathrm{m}})_{\mathrm{nsf}}\, E_0} \tag{2}$$

$$\psi_{\mathrm{sf}} = \frac{\sigma_{\mathrm{sf}}\, d_{\mathrm{sf}}}{(E_{\mathrm{m}})_{\mathrm{sf}}\, E_0} \tag{3}$$

Assuming the physical membrane characteristics (*i.e.* thickness, shape, size, *etc*) in the 2 groups are similar, and since the urine samples of the 2 groups were tested under identical physical conditions of temperature, pressure, *etc*, the charge density σ in each group can be taken as proportional to the respective SEC of the group (Manocha *et al.*, 1987). Thus

$$\frac{\sigma_{\mathrm{nsf}}}{\sigma_{\mathrm{sf}}} \simeq \frac{\mathrm{SEC\ (NSF)}}{\mathrm{SEC\ (SF)}} \simeq 2$$

Hence

$$\frac{\psi_{\mathrm{nsf}}}{\psi_{\mathrm{sf}}} = \frac{2(E_{\mathrm{m}})_{\mathrm{sf}}}{(E_{\mathrm{m}})_{\mathrm{nsf}}} \tag{4}$$

Two cases arise: either $\psi_{\mathrm{nsf}}=\psi_{\mathrm{sf}}$, in which case $(E_{\mathrm{m}})_{\mathrm{nsf}}=2(E_{\mathrm{m}})_{\mathrm{sf}}$, or $(E_{\mathrm{m}})_{\mathrm{nsf}}=(E_{\mathrm{m}})_{\mathrm{sf}}$, in which case $(\psi_{\mathrm{nsf}})=2\,\psi_{\mathrm{sf}}$.

Thus, either the dielectric constant of non-stone formers' solute transfer system is double that of stone-formers, or the potential across the stone formers' solute transfer system (ψ_{sf}) is half. In the latter case the quantitative transfer of solute in stone formers should have been impaired (which is not the case), while in the former the combination of charges (qualitative changes) should take place within the transfer system. This may explain the presence of calcium oxalate deposits in the stone former's transfer system in the kidney (Carr, 1954). This study also supports the earlier analysis that the dielectric constant of stone formers' urine is decreased by a combination of charges. As to why the dielectric constant is decreased in stone formers

Table Specific Electrical Conductivity (µmho/cm) of Urine and Serum at 37°C and 50 Hz

	Group I (Stone Formers)			*Group II (Non-Stone Formers)*		
Sample	*Minimum*	*Maximum*	*Mean ± SD*	*Minimum*	*Maximum*	*Mean ± SD*
Urine	0.47×10^4	1.5×10^4	$1.05 \times 10^4 \pm 0.28 \times 10^4$	0.9×10^4	3.33×10^4	$2.29 \times 10^4 \pm 0.51 \times 10^4$*
Serum	1.17×10^4	1.26×10^4	$1.23 \times 10^4 \pm 0.03 \times 10^4$	1.17×10^4	1.23×10^4	$1.20 \times 10^4 \pm 0.03 \times 10^4$†

* $P<0.001$
† $P>0.05$

during the process of transfer of solute across the membrane, further investigation is warranted.

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Magnetic Resonance Imaging of Renal Carcinoma with Extension into the Vena Cava: Staging Accuracy and Recent Advances

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Summary—In 16 patients with surgical confirmation of inferior vena cava thrombi from renal carcinoma, magnetic resonance imaging (MRI) and computed tomography (CT) were compared to assess the ability of non-invasive, cross-sectional imaging techniques to detect tumour thrombus, the level of its extension, and vessel wall invasion. MRI accurately detected tumour thrombus in the inferior vena cava in all 16 cases (CT in 14) and demonstrated the cephalad extent of tumour thrombi in 15 of 16 (CT in 11). The level of extension was more easily seen on MRI, as was the presence of extension into the hepatic veins—a finding not detected by CT. Tumour invasion of the wall of the inferior vena cava was correctly demonstrated in 7 cases on MRI and in 1 case on CT. In 8 of 16 patients, gradient recall acquisition in steady state (GRASS imaging) was performed in addition to conventional spin echo sequences and it correctly identified the composition of thrombus in all: tumour in 6 patients, blood clot in 1 and both tumour and blood clot in the remaining patient.

MRI and CT are excellent for detection of tumour but MRI is superior in the evaluation of vascular extension. In addition, the use of GRASS imaging allows differentiation of tumour from blood thrombus.

Renal carcinoma will extend into the renal vein and inferior vena cava (IVC) in approximately 25 and 10% of cases respectively (Clayman *et al.*, 1980). Such extension does not preclude surgery, as 5-year survival rates vary between 20 and 50% in patients without lymph node or distant metastases who undergo nephrectomy and thrombus extraction (Clayman, *et al.*, 1980; Pritchett, *et al.*, 1986). The success of such procedures is dependent on the level of vascular extension and the presence of vessel wall invasion. Patients with extensive or invasive tumours may require cardiopulmonary bypass, circulatory arrest or vena cava resection for complete tumour resection. An accurate assessment of the level of venous extension as well as the presence of tumour invasion of the vena cava wall is important because it facilitates the proper choice of incision and anticipation of the ancillary vascular manipulation necessary for safe and complete tumour extraction and vascular reconstruction.

Inferior venacavography has been the imaging technique most often used for assessing vascular extension by renal carcinoma. Ultrasound and computed tomography also have been shown to detect the presence and extent of vena cava thrombi. Magnetic resonance imaging may be especially useful in such cases because of its capacity for multiplanar imaging and ability to image vascular structures and characterise blood flow (Sechtem *et al.*, 1987). In addition, the use of new imaging techniques—gradient recall acquisition in the steady state (GRASS)—might allow differentiation of blood clots from malignant thrombi.

The present study was undertaken to determine whether MRI can stage and detect vascular extension by renal carcinoma, characterise thrombus composition, and differentiate tumour adherence from vessel wall invasion.

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Patients and Methods

This retrospective study (from 1984 to 1990) included 5 women and 11 men (aged 40 to 74 years) with extension of renal carcinoma into the IVC. All patients underwent surgical exploration. In 15 the primary tumour was in place, and the remaining patient had been referred for evaluation 7 months after a radical nephrectomy for what was thought to be localised renal carcinoma. All patients underwent CT and MRI before surgery. The scans were reviewed by 2 of the authors (L.M. and H.H.) without knowledge of the surgical findings. Images obtained by both techniques were assessed for the presence of tumour thrombus, its level (including any extension into the contralateral renal vein or hepatic veins), vessel wall adherence or invasion, and local tumour staging (lymph node metastases, capsular penetration, contiguous organ involvement). The cephalad extent of the tumour thrombus was assessed as follows: infrahepatic, intrahepatic (below the hepatic veins), infradiaphragmatic (at or above the hepatic veins), supradiaphragmatic, or atrial. CT and MRI results were compared with surgical and pathological findings.

Imaging techniques

Magnetic resonance scans were performed on a 0.35 T superconducting magnet (Diasonics), on a General Electric Sigma 1.5 T superconducting magnet, or a Picker 1.5 T superconducting magnet (1 patient). Transaxial scans were obtained in all 16 patients, coronal scans in 15 and sagittal scans in 5. T_1-weighted images were acquired with a recovery time (TR) of 700 ms or less and an echo time (TE) of 30 ms or less, T_2-weighted images with a TR of 2000 ms or more and a TE of 60 ms or more. Slice thickness was 10 mm with a 2-mm gap in all patients. Additional 5-mm slices in the transaxial plane at the level of the renal veins were obtained in 10 patients at 1.5 T. In addition, breath-hold single-slice GRASS images were obtained in 8 (TR = 33 ms; TE = 13 ms; flip angle 30°). In 6 patients additional cardiac-gated GRASS images through the heart were obtained.

Fifteen patients underwent CT scanning with and without contrast (in the remaining patient, CT was performed without contrast only, owing to a medical contraindication). At this institution 3 scans were obtained with the GE 9800/CT/T scanner with a 10-mm slice thickness. The remaining scans were obtained at several different institutions with current scanning techniques and slice thicknesses of 10 mm (n = 9), 8 mm (n = 1) or 5 mm (n = 1).

On CT, thrombus in the IVC was diagnosed when a low-attenuation filling defect was seen within the lumen (Fein *et al.*, 1987). When thrombus filled the entire lumen, the IVC diameter was often increased focally. Contrast injection enhanced the thrombus. When blood flow obstruction was incomplete, the intraluminal enhancement was peripheral and ring-like (so-called "doughnut-like"). Focal wall enhancement or infiltration of adjacent soft tissue indicated vena cava wall invasion. Collateral vessels were often identified in the retroperitoneum.

On MRI, tumour thrombus in the IVC was diagnosed when signal was seen on sequential non-entry sections on both T_1- and T_2-weighted images. Slow flow, which can also give rise to a signal in the blood vessel, was differentiated from a thrombus by detection of the even-echo rephasing phenomenon, which was present only in the former, or by additional imaging with the GRASS technique. To ensure accurate MRI analysis of vessels, the 2 entry sections on the caudal and cranial sites of the imaging volume were disregarded, as an intraluminal signal (owing to flow enhancement) is frequently observed at these levels (Carr and Purcell, 1954). The cephalad extent of the thrombus in the IVC was detected on the sequential transaxial scans and on sagittal and/or coronal images (Figs 1 and 2). Hepatic vein extension was evident on transaxial and coronal scans (Fig. 3). The presence of flow in the IVC was diagnosed by a rim of flow void peripheral to the thrombus (Fig. 4). Invasion of the wall was suspected when, on T_1-weighted images (long TR and TE), definition of the low-intensity wall was obscured (Fig. 1). Invasion was also diagnosed when the tumour signal appeared to extend into adjacent parenchyma (Fig. 5). On GRASS images, blood flow was apparent as a high-intensity signal within the IVC. Thrombus was considered to be composed of blood clot alone when it demonstrated a low signal intensity, tumour when it demonstrated the medium signal intensity similar to that of the primary lesion (Fig. 6). The wall of the IVC on GRASS images has a low signal intensity, and mural invasion was diagnosed when the low-signal-intensity line of the normal vessel wall was no longer seen.

Results

The extent of vascular invasion by renal carcinoma is summarised in Table 1, the extent of surgery in Table 2. Fourteen of the 15 patients with the primary tumour in place underwent radical neph-

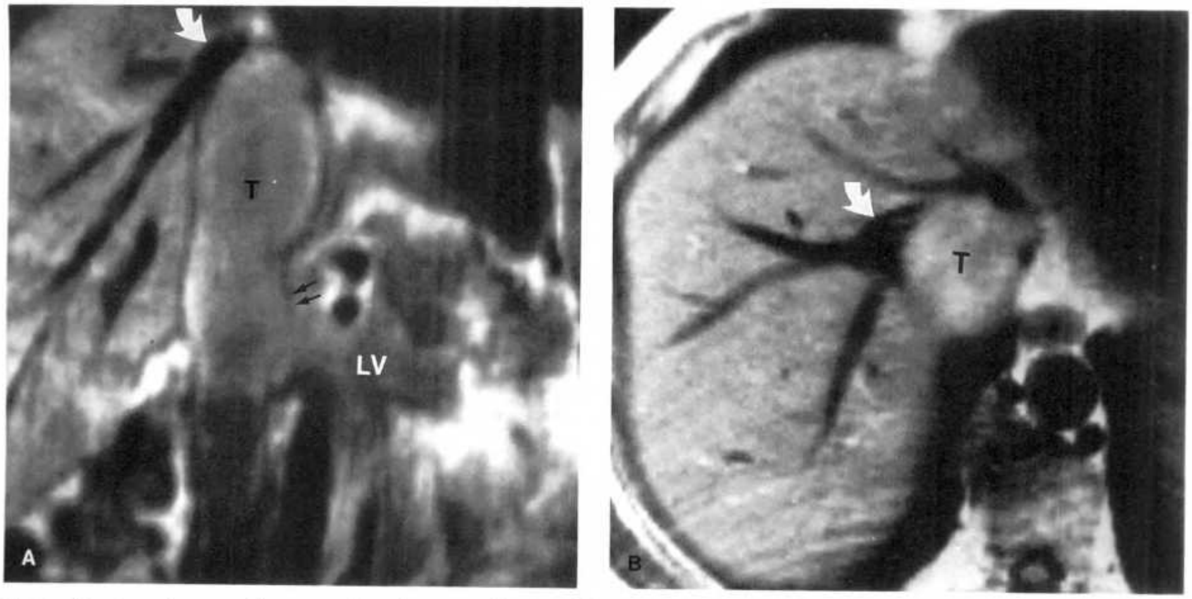

Fig. 1 Renal carcinoma with tumour thrombus extension into left renal vein (LV) and the hepatic portion of the inferior vena cava (T) just below the major hepatic veins. T_1-weighted 0.35 T images: (A) coronal and (B) transaxial scan. The tumour thrombus is invading the left lateral wall of the inferior vena cava (small arrows). Middle hepatic vein (curved arrow) has normal flow.

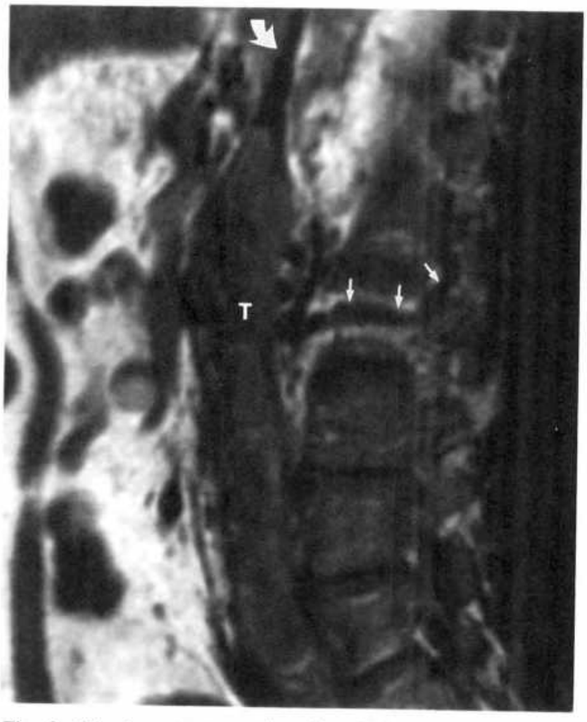

Fig. 2 The large tumour thrombus (T) in the extrahepatic inferior vena cava demonstrated on the sagittal, T_1-weighted, 1.5 T image. Normal flow in the intrahepatic inferior vena cava (curved arrow) is seen. Small white arrows represent the lumbar collateral vessels.

rectomy. Extraction of tumour thrombus from the IVC was accomplished in 13 cases. Encasement of, and invasion into, the vena cava was apparent in 3 patients, 2 of whom had the primary tumour in place and 1 of whom had undergone previous radical nephrectomy, which precluded thrombus extraction.

Surgical findings and pathological staging of the primary tumour in the 14 patients who underwent nephrectomy are summarised in Table 3. Tumour extended to the contralateral renal vein in 2 patients (Fig. 7), to the renal artery in 1, and to the gonadal vein in 2. Hepatic vein extension of the thrombus was confirmed in 2 patients. Capsular penetration was seen in 6 cases. Four patients had metastatic involvement of regional lymph nodes (Fig. 7). Tumour metastasis was seen in 1 case to the opposite kidney and direct spread to the right lobe of the liver in 1 patient. Invasion of vessel wall was noted in 7 cases (vena cava = 5, renal vein = 1, hepatic vein = 1).

The ability of CT and MRI to characterise the local and regional tumour stage (T stage) correctly is summarised in Table 3. In 1 patient, liver metastasis (M stage) suspected on CT was not present at surgery; in another, invasion of the crus of the diaphragm suggested on MRI was not confirmed at surgery.

The presence of thrombus in the IVC was

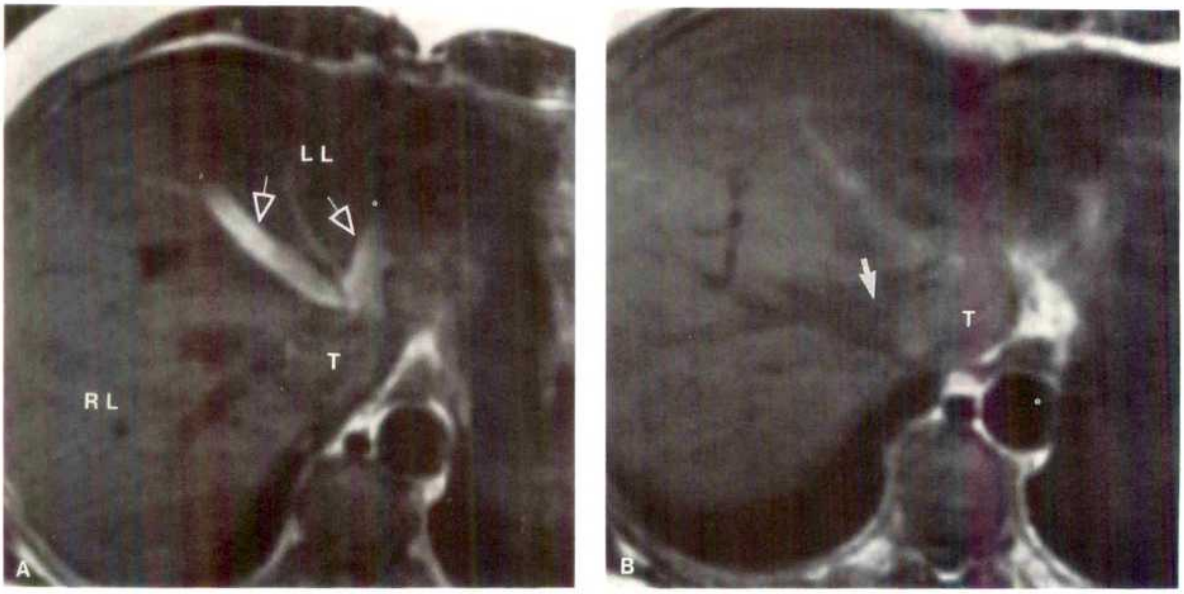

Fig. 3 Tumour thrombus (T) in the hepatic portion of the inferior vena cava extending into (straight arrow) and above the hepatic veins. Proton density, 1.5 T image; (A) and (B) are 2 consecutive transaxial sections. Tumour extension into the right hepatic vein is noted (arrows). The high signal intensity indicates slow flow in the middle and left hepatic vein (open arrows). Also evident is liver vascular congestion, as the right lobe of the liver (RL) is of higher signal intensity than the left (LL).

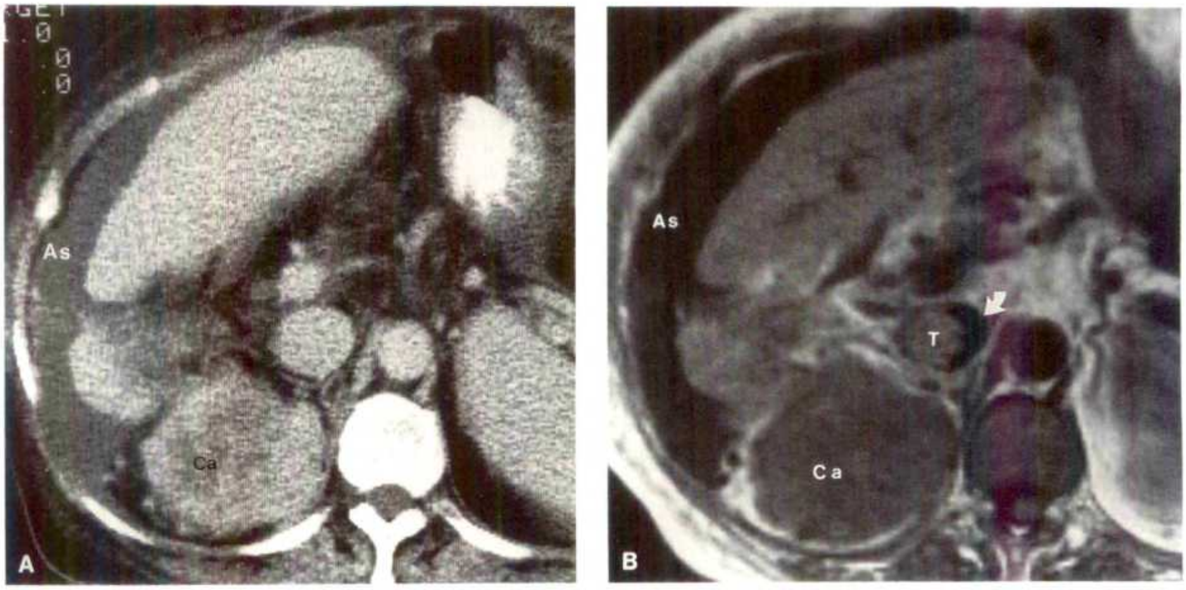

Fig. 4 Right-sided renal carcinoma (Ca) with tumour extension in the extrahepatic portion of the inferior vena cava: (A) CT and (B) corresponding T_1-weighted, 0.35 T MR image. On the CT scan, the inferior vena cava is prominent, but no difference in density to indicate the presence of tumour thrombus is seen. On the accompanying MRI scan, tumour thrombus (T) is seen in the inferior vena cava with the residual flow seen along its right lateral margin (curved arrow). Ascites (As) is also noted.

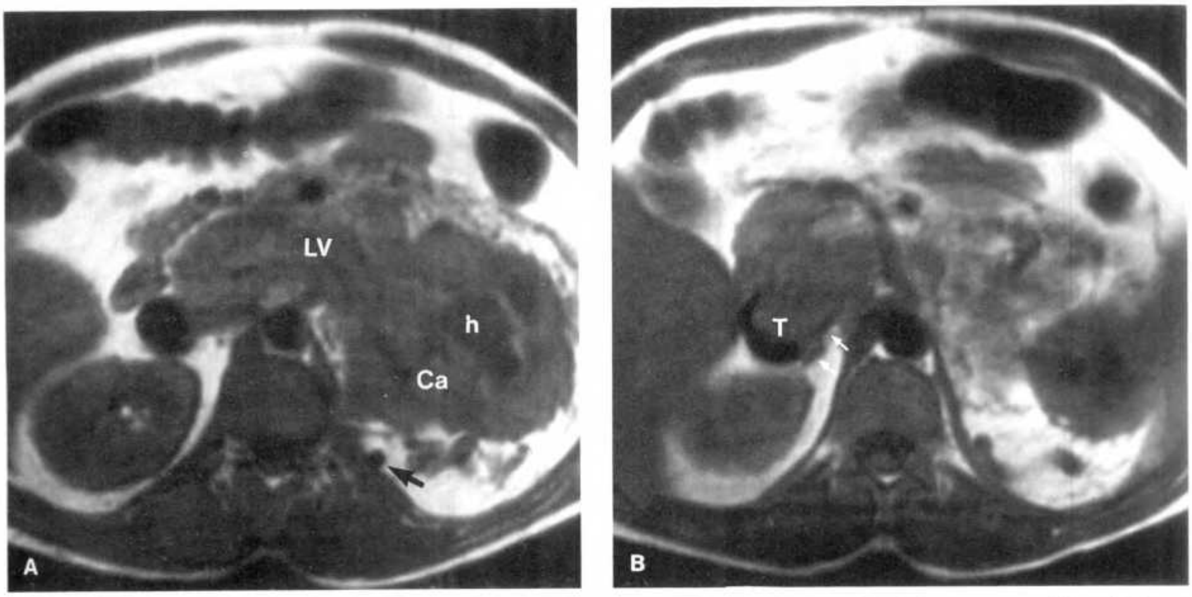

Fig. 5 Left-sided renal carcinoma (Ca) with tumour extension into the left renal vein (LV) and inferior vena cava; (A) and (B) are T_1-weighted, 1.5 T transaxial images. The wall of the inferior vena cava is invaded and tumour extension to the pericaval tissue is evident (arrows). Note collateral vessels (black arrow). Hydronephrosis (h).

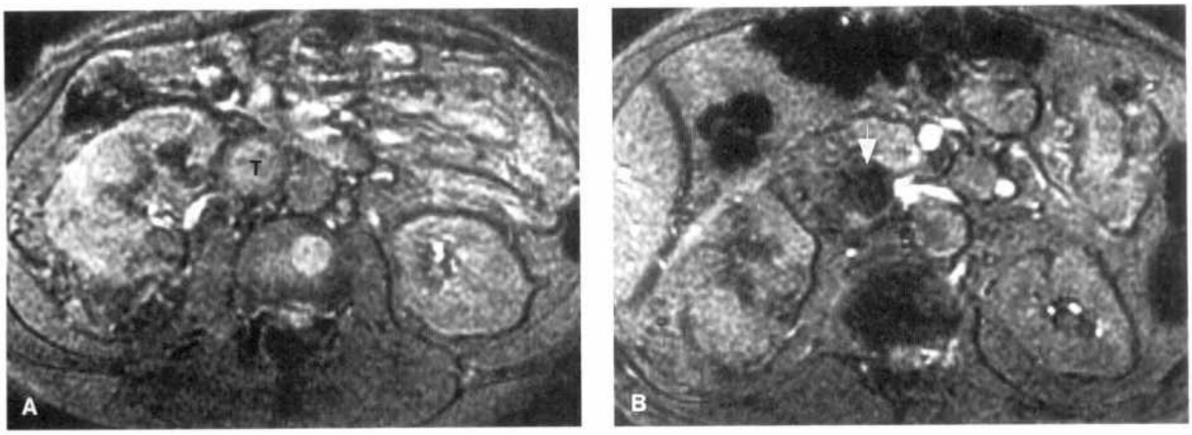

Fig. 6 Renal carcinoma with both tumour (T) and bland (arrow) thrombus in the inferior vena cava imaged with the GRASS technique. Two consecutive levels demonstrate the presence of tumour thrombus with medium signal intensity (A); blood thrombus (arrow) has a low signal intensity (B). The area of high signal intensity in the spine in (A) represents a flow artifact from the aorta.

diagnosed in all cases on MRI and in all but 2 on CT (with and without contrast). In 1 of these 2 patients, the thrombus at surgery was found to be just entering the IVC. In the other patient a small non-obstructing infrahepatic thrombus was not detected. Focal dilation of the IVC had not been apparent, nor was a low-density structure seen within the lumen. CT accurately predicted the upper extent of tumour thrombus in 11 cases, but failed to detect 2 infrahepatic thrombi and was unable to detect the upper extent of 3 others. MRI accurately diagnosed the upper extent of the tumour thrombus in 15 cases, clearly defined the relationship of the tumour thrombus to the insertion of the hepatic veins into the IVC in all (Fig. 1), and detected extension into the hepatic vein in those 2 patients in whom it was confirmed surgically. In 1 patient, the upper extent of the thrombus was thought to be just below the atrium. However, at surgery an intra-atrial thrombus was detected. Cardiac-gated images were not obtained preoperatively. In 1 case, the liver showed image

Table 1 Cephalad Extent of IVC Thrombus

Infrahepatic	7
Hepatic	4
At or below the major hepatic vein	2
Above the major hepatic vein	2
Suprahepatic	5
Infra-atrial	0
Atrial	5

Table 2 Surgical Management of Renal Carcinoma with Vascular Extension

Surgery	*No. of patients*
Radical nephrectomy	14
Extraction of tumour thrombus	13
Cavotomy alone	8
Cavotomy and arteriotomy	5
Right hepatic lobectomy	1
Contralateral partial nephrectomy	1

characteristics suggestive of vascular congestion (Fig. 3). MRI detected extension of the tumour thrombus into the contralateral renal vein in 1 of 2 cases (Fig. 7).

Vessel wall invasion was found at surgery in 7 patients. In only 1 patient did enhancement on CT correctly suggest this finding. On MRI, disruption of the normal, low-intensity wall of the vena cava suggested tumour invasion in 8—*i.e.* 1 false positive. Eight patients had GRASS imaging as well. Mural invasion was correctly predicted in 6 and correctly excluded in 1. Blood clot and tumour thrombus were correctly differentiated in all 8. Malignant thrombus was present in the 6 patients with IVC mural invasion.

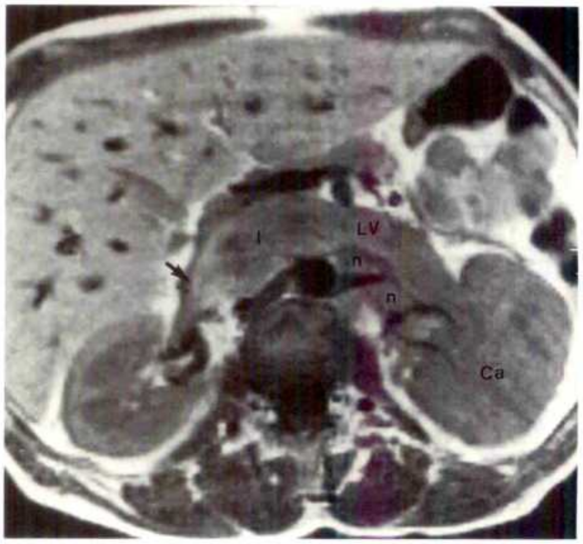

Fig. 7 Left-sided renal carcinoma (Ca) with tumour extension into the left renal vein (LV), inferior vena cava (I) and the right renal vein (arrow). T_1-weighted, 1.5 T image. Also seen are numerous nodes (n) surrounding the left renal artery.

Collateral vessels were seen in 7 cases and were more easily recognised on MRI than CT. In all 7 cases, no flow was detected in the IVC, indicating possible complete occlusion. Gonadal vein thrombus was seen in 2 patients at surgery. In only 1 was it correctly diagnosed; in the other patient, CT and MRI both misinterpreted it as a lymph node in the retrocaval area. MRI and CT correctly diagnosed metastatic regional lymphadenopathy (hilar, periaortic and pericaval) in 3 cases.

Discussion

In patients with renal carcinoma and limited vascular extension, radical nephrectomy and ex-

Table 3 Comparison of Pathological Staging and Imaging

Staging	*Pathological findings (%)*	*CT*					*MRI*				
		TP	*TN*	*FP*	*FN*	*Accuracy (%)*	*TP*	*TN*	*FP*	*FN*	*Accuracy (%)*
Contiguous organ involvement*	1	1	12	1	0	93	1	12	1	0	93
Capsular penetration*	6	4	8	0	2	86	4	8	0	2	86
Lymph node metastases*	4	4	9	1	0	93	4	9	1	0	93
IVC thrombus†	16	14	0	0	2	88	16	0	0	0	100
IVC wall invasion†	7	1	9	0	6	63	7	8	1	0	94

* Based on 14 radical nephrectomy specimens.
† Based on exploration of all 16 vena cava thrombi.
TP = True positive; TN = True negative; FP = False positive; FN = False negative.

traction of tumour thrombus result in a cure rate similar to that in patients without vascular extension (Clayman *et al.*, 1980; Cherrie *et al.*, 1982; Pritchett *et al.*, 1986). Thus careful and accurate pre-operative staging is essential in this group. The objectives of pre-operative imaging include exclusion of distant metastases, an accurate assessment of the presence and level of vascular extension by tumour thrombus, and detection of blood flow within the IVC and vessel wall invasion by tumour thrombus. Such knowledge allows the surgeon to identify patients who would benefit from surgery and to anticipate the use of ancillary anaesthetic and vascular techniques that will allow complete and safe extraction of tumour thrombus. In addition, differentiation of thrombus composition may be especially important when occlusion of the IVC by tumour results in caudad accumulation of blood clot. In such cases, thrombus removal followed by vena caval occlusion, rather than vessel resection or extensive thrombectomy, may be possible.

Inferior venacavography has been the standard imaging technique for evaluating intravascular extension of renal carcinoma. Although accurate, it is invasive, requires infusion of iodinated contrast material, and may need to be supplemented by superior venacavography in patients with complete occlusion of the IVC (Siminovitch *et al.*, 1982; Dorr *et al.*, 1973). Ultrasonography and CT have also been used: their sensitivity for thrombus detection ranges from 68 to 95% and from 60 to 100% respectively (Weyman *et al.*, 1980; Didier *et al.*, 1987; Frohmuller *et al.*, 1987; Johnson *et al.*, 1987). However, either technique may fail to detect small thrombi or to assess the extent of large thrombi accurately. Consequences of the latter limitation can be critical.

Although MRI seems equivalent to CT for the staging of most renal carcinomas, it has significant advantages when contiguous organ involvement or vascular extension is suspected (Hricak *et al.*, 1988). It permits multiplanar imaging and an estimation of vena cava blood flow without the need for injection of iodinated contrast material. Recent experience suggests that MRI can detect vena cava thrombi as accurately as can venacavography (Pritchett *et al.*, 1987; Horan *et al.*, 1989). Horan *et al.* (1989) compared results of pre-operative evaluation by both techniques in 44 patients, 11 of whom had extension into the IVC and 17 into the renal vein. Of the 11 patients with IVC thrombi, both venacavography and MRI correctly identified 9. The authors suggest that they may be complementary and that either may be of limited predictive value when large primary tumours compress the vena cava.

In the present study, MRI was superior to CT for the detection and characterisation of malignant tumour thrombi. These were correctly identified in 16 by MRI, but missed in 2 on CT. However, the thrombi not detected by CT were small and non-obstructing. The cephalad extent of the tumour thrombus and its relationship with the hepatic and contralateral renal vein were clearly visualised by MRI. However, for accurate detection of atrial thrombi cardiac-gated images are necessary. With MRI, assessment was not limited by the size of the thrombus, since in 7 patients the IVC was completely occluded. CT detected vena cava wall invasion in only 1 of 7 cases. It was correctly detected by MRI in all 7, but was suspected in another in which no invasion was found at surgery. In addition, GRASS imaging allowed differentiation of malignant from bland (blood clot) thrombus. Such knowledge cannot be gained from other imaging techniques.

The present study suggests that MRI accurately detects and characterises the extent and composition of venous involvement by renal carcinoma. Although CT and US also will detect the presence of malignant tumour thrombi, MRI may more accurately define the upper extent (including extension into hepatic veins) of large or bulky thrombi. It also determines the presence of vena cava wall invasion better than CT. With the gradient recall echo (GRE) technique, malignant thrombi can be accurately differentiated from blood. Pre-operative knowledge of thrombus composition and vena cava wall invasion is not determined reliably with other techniques. Such knowledge allows the surgeon to advise patients of the possibility of tumour unresectability and to anticipate the type of vascular technique necessary for removal.

In summary, magnetic resonance imaging may be substituted for venacavography when it is available and should be the preferred imaging technique in patients with renal failure or allergies to contrast media.

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15-Hydroxyprostaglandin Dehydrogenase Activity in the Lower Genitourinary Tract

A Preliminary Report

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Summary—In the pathway of prostaglandin inactivation, 15-hydroxyprostaglandin dehydrogenase (15-OHPGDH) has been proven to be the catalyst of the primary catabolic step in the oxidation of the 15-hydroxyl group into a 15-keto moiety in most derivatives of prostaglandins. In this study, we analysed 15-OHPGDH activity in the lower genitourinary tract. The specimens were obtained with permission from patients who underwent surgery. These specimens were then sent for quantitative determination using a tritium release assay specific for 15-OHPGDH. The highest enzyme activity was found in the ureter with a mean ± SE (pmol/min/mg) of 94.99 ± 51.00; the lowest activity was in the vas deferens, with a value of 0.18 ± 0.21. This preliminary study indicated that the activity of 15-OHPGDH in the lower genitourinary tract was significant and that prostaglandin levels in the genitourinary tract may be regulated by this enzyme.

Prostaglandins (PGs) are the metabolic products of polyunsaturated, hydroxylated long chain fatty acid, which can evoke a wide spectrum of biological actions in a variety of tissues. They can be differentiated into several subgroups according to different spatial structures, each expressing a particular type of degree and reaction. Although they differ from each other, most of them are inactivated through the primary catabolic step of the oxidation of the 15-hydroxyl group to a 15-keto moiety—an action catalysed by the enzyme 15-hydroxyprostaglandin dehydrogenase (15-OHPGDH). Two types of 15-OHPGDH are found: one is NAD^+-dependent (Ånggard and Larsson, 1971) and the other is $NADP^+$-dependent (Lee and Levine, 1974). The NAD^+-dependent 15-OHPGDH is primarily responsible for inactivation of PGs *in vivo*, since NAD^+ is the dominant oxidised nucleotide in the cytosol (Hansen, 1976). Because all PGs, with the exception of PGI_2, are rapidly catabolised during a single passage through the lungs, liver and kidneys (Oliw *et al.*, 1983), it is difficult to estimate the exact concentration of PGs in tissues. The activity level of 15-OHPGDH in animal lungs and kidneys (Tai and Yuan, 1977; Chang *et al.*, 1990) and human placenta (Jarabak and Watkins, 1988) has been widely studied. In this study, an attempt has been made to define 15-OHPGDH activity in the lower genitourinary tract.

Patients and Methods

From May 1989 to October 1989, 59 patients were included in the study. There 56 males and 3 females, their ages ranging from 21 to 82 years (mean 64.6). All were undergoing surgery for a variety of urological conditions. The specimen removed at operation was sent for histopathological examination, while at the same time a piece of normal tissue (0.2–1 g in weight) was obtained (with permission) from the ureter, bladder or urethra, as appropriate, together with prostate tissue from patients with either benign prostatic hyperplasia (BPH) or car-

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cinoma, for quantitative analysis of 15-OHPGDH activity.

A tritium release assay was used to determine the enzyme activity of NAD$^+$-dependent 15-OHPGDH (Tai and Yuan, 1977). Immediately after sampling, the tissues were stored in a container kept cool by ice and sent to the laboratory for quantification of 15-OHPGDH activity. The tissues were weighed and then homogenised in 0.1 M potassium phosphate buffer, pH 7.5, containing 1 mM EDTA. The homogenates were centrifuged at 27,000 *g* for 30 min. The supernatant was obtained for quantitative determination by a tritium assay which was specific for 15-OHPGDH. The reaction mixture contained: NH_4Cl, 5 μmol; α-ketoglutarate, 1 μmol; 15(S)-[15-^{3}H]PGE_2, 1 nmol, 30,000 cpm; glutamate dehydrogenase, 100 μg; and tissue supernatant in a final volume of 1 ml of 0.1 M potassium phosphate buffer, pH 7.5, containing 1 mM EDTA. The reaction was continued at 37°C for 10 min; 0.3 ml of charcoal suspension (10% charcoal in 1% dextran) were added to it and the solution was again kept at room temperature for 5 min. The mixture was centrifuged at 1000 *g* for 10 min. Subsequently, 0.4 ml of the supernatant were determined by a Beckman LS 5000 TA scintillation spectrophotometer to quantify the 15-OHPGDH activity. The protein content in the supernatant was determined by the method of Lowry *et al.* (1951) with bovine serum albumin (fraction V) as a standard.

Results

The results of 15-OHPGDH activity are indicated in the Table. The highest enzyme activity was found in the ureter and decreased in the following order: urethra, bladder, prostate tissue from patients with BPH or prostatic carcinoma, seminal vesicle, epididymis, testis, corpus cavernosum and vas deferens. There was no correlation between age and enzyme activity in BPH tissue ($t = 1.220$; $P > 0.05$). There were 43 prostate samples; 34 of these were obtained by transurethral resection (TUR) for BPH and 4 by means of open operation for other diseases, while 5 samples were of prostates with carcinoma obtained by either TUR or radical prostatectomy for localised disease. There was no significant difference in the mean enzyme activity between the TUR samples (11.99 ± 3.92 pmol/min/mg) and the tissue obtained by open operation (20.65 ± 12.37 pmol/min/mg) ($t = -0.71$, $P > 0.05$). There was no significant difference in enzyme activity between the BPH tissue (12.90 ± 3.71 pmol/min/mg) and prostatic carcinoma tissue (12.74 ± 8.24 pmol/min/mg) ($t = 0.01$, $P > 0.05$).

Table Quantitative Analysis of 15-OHPGDH Activity in the Lower Genitourinary Tract

Tissue	*Sample no.*	*15-OHPGDH (mean ± SE pmol/min/mg)*
Ureter	5	94.99 ± 51.00
Bladder	7	14.50 ± 5.80
Prostate (BPH)	38	12.90 ± 3.71
Prostate (prostatic carcinoma)	5	12.74 ± 8.24
Seminal vesicle	4	4.46 ± 2.01
Vas deferens	2	0.18 ± 0.15
Epididymis	1	1.98
Testis	3	1.85 ± 0.99
Urethra	1	28.96
Corpus cavernosum	5	1.00 ± 0.42

Discussion

15-OHPGDH is the primary enzyme in biological inactivation of prostaglandins (Oliw *et al.*, 1983). Our study of tissue from the genitourinary tract has shown that the ureter has the highest 15-OHPGDH activity and the vas deferens the lowest.

Prostaglandins have been shown to play an important physiological role in mediating ureteric motility (Thulesius and Angelo-Khattar, 1985). This has led to the use of prostaglandin synthetase inhibitors in the form of non-steroidal anti-inflammatory agents in the treatment of acute ureteric colic (Holmlund and Sjödin, 1978; Lunstam *et al.*, 1982). In the study by Bauer and Bach (1986), PGE_2 concentration in the prostatic fluid of healthy men was found to be higher than in those with hyperplasia of the prostate. In this study, we had 1 case of a normal prostate without hyperplasia with 15-OHPGDH activity of 9.64 pmol/min/mg, which is lower than that of hyperplastic prostates (12.90 ± 3.71 pmol/min/mg). However, the sample group was too small to estimate whether there was any relationship between PGE_2 concentration in prostatic fluid and 15-OHPGDH activity in healthy or hyperplastic prostate tissue. Further investigation is necessary.

As in other organs, PGs are becoming increasingly recognised as playing an important role in the physiology and pathophysiology of the lower genitourinary tract. Accordingly, the enzyme activity of 15-OHPGDH in the regulation of PGs is also being more extensively studied. However, the extent to which this enzyme takes part and the role it plays in the regulation of PGs remains to be clarified. Further studies are necessary for a better understanding of the nature of 15-OHPGDH and its mechanism of action.

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Bilharzial Vesicoureteric Reflux and Bladder Neck Stenosis: Fact or Fiction?

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Summary—A group of 47 patients with histologically confirmed chronic urinary bilharziasis underwent micturating cystourethrography to look for vesicoureteric reflux (VUR) and bladder neck stenosis (BNS); 13 patients were found to have VUR of varying grades (8 unilateral and 5 bilateral). None had evidence of BNS.

Urinary tract infection (UTI), loin pain, hydroureter and renal failure were compared in patients with and without VUR. Of the 13 patients with reflux, 3 had UTI, loin pain was present in 8, 11 had an ipsilateral hydroureter and 2 presented with renal failure. In the 34 patients without reflux, 8 had UTI, loin pain was present in 22, 30 had hydroureter and 3 presented with renal failure.

It was concluded that the incidence of UTI, loin pain, hydroureter and renal deterioration associated with bilharzial VUR was not significantly different from that found in bilharzial patients without VUR. Thus the clinical significance and the need for surgical correction of isolated VUR in bilharziasis are questionable.

Urinary bilharziasis is an endemic parasitic disease in Saudi Arabia (Arfaa, 1967; Magzoub and Kasim, 1980), especially in the south-western region of Assir (Fayed, 1985). Hydroureter and hydronephrosis due to ureteric strictures are known complications of chronic urinary bilharziasis (Al Ghorab, 1968; Al Shukri and Alwan, 1983). However, other causes of ureteric dilatation have been associated with this disease, *e.g.* ureteric atony (Umerah, 1981), vesicoureteric reflux, stones and bladder neck stenosis (Al Ghorab *et al.*, 1966). Patients with chronic urinary bilharziasis present clinically with loin pain, urinary tract infection and deteriorating kidney function. With such diverse vesical and ureteric pathology, it is difficult to ascertain with accuracy the exact role played by VUR and BNS in these clinical presentations. None of the known surgical procedures seems to be ideal for correction of bilharzial VUR because of extensive fibrosis and gross ureteric dilatation (Al Ghorab *et al.*, 1966). In this prospective study we investigated the clinical significance of bilharzial VUR and BNS and tried to ascertain whether this type of VUR requires surgical correction.

Patients and Methods

The study group comprised 47 patients. Selection was made on the basis of suspicion of the disease from the past history and the results of urine analysis, radiography, serology and cystoscopy. All suspected patients were admitted to hospital and the type of presentation was recorded. Further evidence of the disease was sought by looking for ova of *Schistosoma haematobium* on urine analysis, a significant antibilharzia antibody titre, radiographic features such as vesical calcification, ureteric strictures and spindling and cystoscopic characteristics such as pale mucosa, sandy patches, polyps, ulcers, *etc.* At cystoscopy, calibration of both ureters by ureteric catheters was carried out and all patients with complete obstruction of the ureter were excluded. A bladder biopsy was taken for histological confirmation.

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All patients with histological confirmation of bilharziasis underwent micturating cystourethrography (MCU), looking specifically for VUR and BNS, as described by Edwards and Beggs (1987a and b). Loin pain, urinary tract infection as indicated by a positive urine culture, hydroureter as seen on intravenous urography and biochemical evidence of renal failure were compared in patients with and without VUR. Data were analysed using χ^2 statistics (with Yates correction whenever needed) and SPSS statistical package; 5% was chosen as the level of significance.

Results

Of the 47 patients 1 was a female (aged 30 years). The male patients ranged in age from 18 to 64 years (mean 34.6); 13/47 patients (28%) had VUR on MCU (8 unilateral and 5 bilateral). Details of grades of reflux are shown in Table 1. There was no consistent correlation between the appearance of the ureteric orifice at cystoscopy and reflux, *i.e.* some gaping laterally placed ureteric orifices were not refluxing, and some apparently normal ureteric orifices were found to be refluxing. None of the patients had clinical, radiographic or cystoscopic features of BNS such as severe bladder trabeculation or sacculation. None had a significant reduction in bladder capacity or significant post-micturition residual urine, although 20 patients (43%) had evidence of vesical calcification on X-ray of the kidneys, ureter and bladder.

Correlation of VUR and ipsilateral loin pain (Table 2)

Eight of 13 patients (62%) with VUR had ipsilateral loin pain. However, 22/34 patients (65%) without reflux also presented with loin pain ($P > 0.05$ = not significant).

Correlation of VUR and UTI (Table 3)

Three of 13 patients (23%) with VUR had UTI as evidenced by significant pyuria and/or positive urine culture. Similarly, 8/34 patients (24%) without VUR had UTI ($P > 0.05$ = not significant).

Correlation of VUR and ipsilateral hydroureter (Table 4)

On intravenous urography, 11/13 patients (85%) with VUR had hydroureter on the side of the reflux. However, 30/34 patients (88%) without VUR had dilated ureters on urography ($P > 0.05$ = not significant).

Correlation of VUR and renal failure (Table 5)

Two of 13 patients (15%) with VUR had raised serum creatinine. The first patient had a serum creatinine of 680.7 µmol/l, was undergoing haemodialysis and had bilateral grade IV reflux. The second patient had grade IV VUR on the left side, bilateral lower third ureteric calculi and a serum creatinine of 406.6 µmol/l. In the remaining 11 patients with reflux the 22 kidneys were still functioning even on the early urographic films.

Table 1 Grades of Vesicoureteric Reflux

	Grade I	*Grade II*	*Grade III*	*Grade IV*	*Total*
Unilateral	1	1	1	5	8
Bilateral	1	—	1	3	5
Total	2	1	2	8	13

Table 2 Correlation of Vesicoureteric Reflux and Ipsilateral Loin Pain

		VUR		
		Present	*Absent*	*Total*
Ipsilateral loin pain	Present	8	22	30
	Absent	5	12	17
Total		13	34	47

$\chi^2 = 0.04$ $P > 0.05$ (N.S.)

Table 3 Correlation of Vesicoureteric Reflux and Urinary Tract Infection

		VUR		
		Present	*Absent*	*Total*
Urine culture	Infected	3	8	11
	Sterile	10	26	36
Total		13	34	47

$\chi^2 = 0.001$ $P > 0.05$ (N.S.)

Table 4 Correlation of Vesicoureteric Reflux and Hydroureter

		VUR		
		Present	*Absent*	*Total*
Ipsilateral hydroureter	Present	11	30	41
	Absent	2	4	6
Total		13	34	47

$\chi^2=0.116$ $P>0.05$ (N.S.)

Table 5 Correlation of Vesicoureteric Reflux and Renal Failure

		VUR		
		Present	*Absent*	*Total*
Renal failure	Present	2	3	5
	Absent	11	31	42
Total		13	34	47

$\chi^2=0.426$ $P>0.05$ (N.S.)

On the other hand, in 3/34 patients (9%) without VUR, serum creatinine was raised at 177, 530 and 574.6 µmol/l. All had unilateral ureteric stones and bilateral huge hydroureters.

There was no significant difference between the renal failure rate in patients with refluxing and those with non-refluxing ureters ($P>0.05$).

Discussion

Bilharziasis is an endemic parasitic disease that globally afflicts more than 200 million people; a further 600 million are known to be at risk. The disease is common in Saudi Arabia (Wallace, 1979) and many other Middle Eastern countries. It is also endemic in Africa, South America and South-East Asia. In humans, urinary and intestinal forms are known. In the urinary type the disease is transmitted through the intermediate host Bulinus snail. It affects mainly the urinary bladder and lower ureters. In the chronic stage fibrosis with chronic infection takes place and patients present with features of obstructive uropathy, the commonest cause of which is lower ureteric strictures (Al Shukri and Alwan, 1983). On urography these patients usually have widely dilated, tortuous ureters with mechanical obstruction mostly at the vesicoureteric junction, but also occasionally elsewhere along the ureter. Treatment of these strictures is best achieved by resection anastomosis in the upper and middle ureter (Awad *et al.*, 1989). However, at the vesicoureteric junction, ureteroneocystotomy gives the best results, although some advocate regular endoscopic dilatation (Umerah, 1981; Jacobsson *et al.*, 1987).

Vesicoureteric reflux occuring in as many as 44.3% of bilharzial patients has been reported as another cause of hydroureter (Al Ghorab *et al.*, 1966). The exact cause of reflux in bilharzial ureters is not clearly understood. The anti-reflux mechanism is perhaps disturbed because of failure to compress the rigid fibrous transvesical course of the ureter during bladder contraction. Moreover, chronic infection and shortening of the transvesical ureteric course owing to fibrosis are said to be additional contributory factors (Al Ghorab *et al.*, 1966). VUR was present in only 28% of our patients, which contrasts with the frequency of 44.3% reported by Al Ghorab *et al.* (1966). The difference could be due to geographic, socio-economic and ethnic factors which are known to affect the severity and pattern of the disease in different parts of the world.

Bilharzial VUR is difficult to treat. The known standard surgical procedures that suit other types of VUR are not ideal in view of extensive fibrosis, chronic inflammation and gross ureteric dilatation (Al Ghorab *et al.*, 1966). VUR may present clinically as loin pain which is aggravated by micturition. The reflux can result in infection, progressive hydronephrosis and renal damage. We have therefore studied these 4 criteria in depth (loin pain, UTI, hydroureter and renal failure) to evaluate the clinical significance of bilharzial VUR.

Loin pain was present in 62 and 65% of our patients with and without VUR respectively. As far as this symptom is concerned, therefore, it could be said that VUR did not contribute greatly to the morbity in the group studied. UTI was found in 23 and 24% of our patients with and without VUR respectively. Thus it seems that VUR did not cause our patients to be significantly more susceptible to UTI.

On urography, 85 and 88% of our patients with and without reflux had hydroureter respectively. The dilated ureter is an important radiographic feature of urinary bilharziasis and it is not necessarily caused by VUR alone in unobstructed ureters. Ureteric atony diagnosed by fluoroscopic screening has been shown to occur in bilharziasis and can cause hydroureter (Umerah, 1981). We believe that many bilharzial ureters undergo dilatation even though they are not refluxing, atonic or obstructed by strictures or stones. Indeed, in some of our patients disorganised peristaltic waves incapable of transmitting urine along the ureter were seen under fluoroscopy. This ambiguity may be resolved by further histochemical studies of bilharzial ureteric segments using electron microscopy. Of our patients with and without reflux, 15 and 9% respectively presented with renal failure ($P > 0.05 =$ not significant). None of the remaining patients with reflux had a radiologically functionless kidney attributed to isolated reflux. When kidney function deteriorates in bilharziasis it is due to a multitude of factors, such as stasis, infection and obstruction caused by several other complications of bilharziasis.

Our results indicate that the clinical significance of VUR in bilharzial patients is questionable. Al Ghorab *et al.* (1966) also failed to define a clinical syndrome which is characteristic or even suggestive of reflux in bilharziasis, although advocating the design of a new type of operation to correct vesicoureteric reflux in bilharzial patients. On the contrary, we believe that isolated bilharzial VUR adds little to the morbidity and should be treated conservatively since surgical correction is extremely difficult.

BNS has been previously reported in bilharzial patients (Al Ghorab, 1968). Admittedly, the diagnosis of BNS is never complete without urodynamic studies, including uroflowmetry. These studies were not carried out in our patients because none of them had symptoms or signs of bladder outlet obstruction. In addition, cystoscopic and radiographic features of this complication were not seen to justify further bladder studies. It is possible that BNS was either over-emphasised in the past or is only seen elsewhere in the world in patients with severe vesical fibrosis and contraction, a situation which did not arise in our patients.

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Para-urethral Collagen Implantation for Female Stress Incontinence

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Summary.—A series of 25 women with genuine stress incontinence were treated by para-urethral injection of glutaraldehyde cross-linked collagen. The technique was simple and associated with few complications. Follow-up at 3 months revealed 20 patients (80%) to have been symptomatically improved or cured. An increase in urethral closure pressure together with a decrease in urine flow rate and increase in detrusor pressure was found post-operatively. The success rate was significantly higher (90%) in patients who had undergone previous surgery for urinary incontinence when compared with those who had had no previous surgery (73%).

Female genuine stress incontinence (GSI) results from bladder neck hypermobility and/or intrinsic urethral sphincter weakness. Surgical attempts to restore continence aim to elevate the bladder neck into the abdominal zone of pressure and to increase urethral closure pressure during stress. Urethral pressure augmentation without additional elevation of the bladder neck has previously been considered an option for those patients with a normally sited bladder neck and leakage secondary to urethral sphincter weakness.

The concept of directly bolstering the urethra by means of an injectable compound is an attractive one, although not new. Murless (1938) injected sodium morrhuate around the urethra but the procedure was abandoned owing to a high incidence of embolism of the material from the periurethral spaces resulting in pulmonary infarction. Several authors have described the use of Teflon paste for treating patients with GSI. The cure rates ranged from 21 to 75% (Politano *et al.*, 1974; Lim *et al.*, 1983; Schulman *et al.*, 1983, 1984). However, the use of Teflon was associated with several problems: it was difficult to administer, requiring injection at high pressure through a large bore needle; submucosal extrusion of the paste was frequently observed and, in experimental animals, Teflon particles had been found to embolise from the injection site to lungs, liver, spleen and brain (Malizia *et al.*, 1984).

Purified bovine and porcine collagen has been used in a number of clinical applications, *e.g.* artificial skin, cardiac valve prostheses, vascular prostheses and implants in plastic surgery (Chvapil *et al.*, 1973). An injectable collagen gel extracted from bovine skin has been available for several years (Kaplan *et al.*, 1983). However, the initial preparation which was used to correct skin deficits in plastic surgery produced only a temporary improvement and histologically was shown to have been mostly resorbed by 90 days (Kligman and Armstrong, 1986). A second generation derivative is now available in which the collagen fibrils are cross-linked with glutaraldehyde. Human *in vivo* skin studies have demonstrated that this preparation encourages the host to replace the collagen implant with endogenous collagen (Kligman and Armstrong, 1986). This cross-linked preparation might therefore be expected to produce a more permanent bolstering in soft tissue. To this end, we have evaluated its use in the treatment of female genuine stress incontinence.

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Patients and Methods

Twenty-seven women with urodynamically proven genuine stress incontinence were entered into the study. Their mean age was 52.3 years (range 34–79). All were shown by pad testing (Richmond *et al.*, 1987) to have significant urinary leakage, *i.e.* >2 ml. Ten patients had previously undergone failed incontinence operations (4 had 1 previous procedure, 3 had 2 previous procedures and 3 had 3 previous procedures). The remaining 15 had no previous incontinence surgery.

An intradermal skin injection of 0.1 ml collagen was administered into the volar surface of the forearm 1 month prior to para-urethral injection. Two patients showed a positive response to the skin test, implying hypersensitivity to the collagen product, and were excluded from the trial.

The initial 8 procedures were carried out under a general anaesthetic and the remaining 17 under local anaesthesia 30 minutes prior to arrival in theatre for local anaesthetic, a topical para-urethral application of lignocaine cream (Elma, Astra Pharmaceuticals, Kings Langley, England) was applied by the patient. Antibiotics were not given. Stress incontinence was confirmed by asking the patient to cough with the bladder filled. Cystourethroscopy was performed and an open bladder neck was seen in all patients. A 9 cm, 20 gauge needle was placed 0.5 cm lateral to the external urinary meatus and passed up to the bladder neck. Under cystoscopic control, collagen was injected in aliquots of 2.5 ml into the periurethral tissues immediately below the bladder neck, at the 3 and 9 o'clock positions. Care was taken to avoid penetrating the urethral lining. Sufficient collagen was injected to produce urethral buttresses resulting in gentle apposition of the urethral lumen. Injections at the 12 and 6 o'clock positions were given if there was insufficient apposition of the urethra. After injection, the patients were requested to cough again with a full bladder to confirm cessation of leakage. The bladder was emptied with a 9 F catheter so as to cause minimal disruption to the collagen buttresses. The patient was allowed to leave hospital once voiding was established.

Follow-up was by symptomatic questioning and pad testing at 1 month. Those patients not rendered completely continent were re-treated with further collagen. Three months after their last collagen injection, urodynamic evaluation was repeated.

Results

Eighteen patients (72%) required re-treatment after their initial injection. At the end of the treatments the patients' results were analysed subjectively and objectively.

The following symptomatic definitions were made:

Cure:	complete cessation of stress incontinence.
Improvement:	reduction in the degree of stress incontinence but the patient still requiring to change underclothes or wear protection.
Failure:	no significant improvement in symptoms.

On these criteria, there was a cure rate of 64% and a success rate of 80% (obtained by including all of those patients who were either cured or improved) (Table 1). The success rate was higher in patients who had had previous surgery (90%) than in those who had not (73%). The failures in the previously untreated group included a patient who had received pelvic radiotherapy for carcinoma of the endometrium. The failure in the previous surgery group was a markedly obese lady whose weight precluded her from any other operative procedure.

Pad testing revealed a significant decrease in the quantity of leakage after injection (Table 2).

Stress urethral profiles were abnormal or equivocal in 19 patients before injection (76%). After injection, 11 (44%) were still abnormal or equivocal and 4 of these were cured. The correlation between normal stress profile and a symptomatic cure was not significant.

Comparison between urodynamic parameters before and after injection in those patients symptomatically cured (Table 3) revealed an increase in maximum urethral closure pressure and a decrease

Table 1 Subjective Response to Collagen Injection in 25 Patients

	No	*Cure (%)*	*Improvement (%)*	*Success (%)*	*Failure (%)*
No previous surgery	15	8 (53)	3 (20)	11 (73)	4 (27)
Previous incontinence surgery	10	8 (80)	1 (10)	9 (90)	1 (10)
Total	25	16 (64)	4 (16)	20 (80)	5 (20)

Table 2 Extended Pad Test Results Before and After Injection

	Before injection	*After injection*
Range (ml)	218.0–2.0	100.0–0.1
Mean (ml)	46±13.0 SEM	16.9±5.28 SEM
Median (ml)	13 7	1.6

Method based on Sutherst *et al.* (1987).

Table 4 Complications of Para-urethral Collagen Injection

No. of patients	*Complication*
2	Procedure abandoned as patient unable to tolerate procedure under local anaesthesia
1	Presumed bacteraemia and hypothermia
1	Coliform urinary tract infection
1	Anterior wall vaginal abscess
3	Urinary retention requiring intermittent self-catheterisation for 12–72 h

in functional urethral length. On voiding there was an increase in maximum detrusor pressure and a decrease in urine flow rate in keeping with an iatrogenic infravesical obstruction. Of these changes only the increase in detrusor pressure reached significance (Wilcoxon's matched pairs). One patient only developed detrusor instability post-operatively.

There was a significant correlation between symptomatic cure and absence of urinary leakage during the filling cystometrogram.

Eight patients encountered complications (Table 4). The vaginal abscess occurred in the obese patient from the previous surgery group. She re-presented unable to pass urine 3 days following injection. The abscess ruptured spontaneously and she was able to pass urine again, but her stress incontinence reoccurred immediately. After injection, only 2 patients (8%) had to remain in hospital overnight: 1 with hypothermia consequent upon a presumed bacteraemia and 1 with urinary retention who was unable to master self-catheterisation. The 3 patients who were unable to pass urine post-operatively required no more than 3 days of self-catheterisation before spontaneous voiding was re-established.

Discussion

Para-urethral collagen injection is a straightforward technique which can be performed as a day case procedure under local anaesthesia. It is associated with few complications and can readily be repeated should the result from the first injection not be satisfactory. The mechanism by which collagen injection restores continence is probably by an increase in urethral closure pressure and not, somewhat surprisingly, by an increase in functional urethral length. The failure of these results to reach significance is probably related to the relatively small numbers involved. The significant increase in outflow resistance produced by the collagen is reflected by a significant increase in detrusor pressure and a fall in urine flow rate.

The higher success rate in those with failed previous incontinence surgery may result from these patients having a less hypermobile bladder neck consequent upon the scarring effect of their previous surgery tethering the bladder neck in a more stable position.

There is undoubtedly a significant learning curve in this technique, the later patients recruited having noticeably better results. Judgement of needle placement and the amount of collagen to inject will improve as greater experience with the technique is gained.

Longer follow-up of these patients is essential to determine how permanent is the effect of the injected collagen. Should follow-up reveal a consist-

Table 3 Urodynamic Parameters in 16 Women Cured by Collagen Injection

	Before injection (MEAN±SEM)	*After injection (MEAN±SEM)*	*Percentage difference*
Bladder capacity (ml)	501±34.3	504±39.9	+0.5
First desire to micturate (ml)	328±42.3	347±25 0	+6
Maximum detrusor pressure (cm H_2O)	18.2±3.38	30.4±3 96	+67*
Maximum urine flow rate (ml/s)	18 7±2.22	17.0±1.23	−10
Maximum urethral closure pressure (cm H_2O)	35.3±3.62	39.6±3.83	+12
Functional length of urethra (cm)	2 89±0.16	2.85±0.11	−10

*$P<0.5$ Wilcoxon's matched pairs test.

ent improvement, this promising technique may have a role not only in first-line treatment of stress incontinence but also in cases where conventional surgery has failed or is best avoided.

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Bladder Augmentation and Replacement

Urodynamic and Clinical Review of 25 Patients

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Summary—Bladder augmentation has a role in the management of patients with neuropathic bladder dysfunction and in urinary undiversion. Several reports attest to its clinical value, but there have been few detailed urodynamic studies of its effects. We have carried out a prospective review over a 4-year period of 25 patients undergoing bladder augmentation or substitution assessed by conventional and ambulatory urodynamic studies. All patients had a detubularised reservoir made of ileum in 6, and of the ileocaecal segment in the remainder. Six patients also had an artificial sphincter fitted and 2 underwent colposuspension.

There was no mortality. After operation, bladder capacity increased from 122±91 ml to 659±431 ml and there were significant decreases in the pressure rise during filling and increases in bladder compliance. Hyper-reflexia was present in 74% before operation and 23% after operation. Regular phasic activity was observed in 77% of patients at the end of filling after operation, probably due to bowel activity despite detubularisation. Four patients described urge incontinence associated with this activity.

After operation, one man had persistent major stress incontinence. He has since undergone insertion of an artificial urinary sphincter (AUS) and is now completely dry. Of the remainder, 10 patients had minor, infrequent defects in continence, 9 patients with leakage when the bladder was full and 4 with occasional leakage at night. With the exception of the patient with major stress incontinence, all but one felt the operation had been worthwhile—40% reporting complete success and 52% excellent improvement. Reconstruction of the neuropathic lower urinary tract is a major surgical procedure, but the final clinical outcome is very satisfactory.

A small capacity bladder may be the sequel of many disease processes and for many years some patients have been managed by means of augmentation with intact bowel segments. The first report of the technique was Mikulicz (1899), who described the use of ileum. During the 1950s and 1960s the operation became frequently used for tuberculosis, and several large retrospective series have been reported (Kuss *et al.*, 1970; Dounis *et al.*, 1980). Many different bowel segments have been tried, but usually the intact caecum has been used. Yeates (1956) described the use of detubularised ileum and this method has since been shown to be an effective method of providing a highly compliant reservoir for augmentation (Schmidbauer *et al.*, 1987; Weinberg *et al.*, 1988), having a significant decrease in peristaltic activity compared with tubular segments (Light and Engelmann, 1985). More recently, the use of bladder augmentation has been explored in the neuropathic bladder, when it may need to be combined with techniques to increase outflow resistance such as artificial sphincter placement or colposuspension. The use of clean intermittent self-catheterisation has proved to be an important advance, for it has permitted such patients to empty their bladders reliably (Lapides *et al.*, 1972; Webb *et al.*, 1990). These techniques are now also finding

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a role in providing bladder replacement for selected patients undergoing radical cystectomy for urothelial malignancy (Mundy *et al.*, 1986; Wenderoth *et al.*, 1990). The use of the detubularised segment with lower peristaltic pressures is probably of great importance in these cases, particularly after radical cystoprostatectomy, where the outlet resistance may be significantly diminished.

Many of the published series have related to bowel segments used in both tubularised and detubularised form, but urodynamic data have been scarce and often incomplete. We therefore decided to undertake a prospective urodynamic and clinical study of both bladder augmentation and replacement using detubularised ileal or ileocaecal bowel segments with the aims of characterising the urodynamic results of operation and correlating these findings to the clinical outcome.

Patients and Methods

Twenty-five patients were studied (15 men, 10 women; mean age 34 years, range 16–72) who had undergone bladder augmentation and replacement since 1986. A urodynamic review was undertaken at a mean of 14 months after operation (range 2–42 months). The operation was performed for a variety of conditions: 19 patients had neurogenic bladder dysfunction (16 spina bifida, 2 spinal neoplasms and 1 spinal trauma), of whom 7 underwent urinary undiversion procedures (Table I). Two of these 19 patients were undergoing revisionary operations for failed bladder augmentation procedures performed several years previously, where the bowel segment was still causing persistent phasic activity and resulting in troublesome incontinence: in one patient the caecal segment had not been detubularised and the other patient had a detubularised sigmoid segment. Two men underwent simultaneous radical cystoprostatectomy and lymphadenectomy for transitional carcinoma of the bladder (1 T3 and 1 T2 tumour), 2 patients had interstitial cystitis and 2 had severe bladder contraction as a result of tuberculosis.

In all patients the bowel segment was detubularised. In 6 patients the bowel segment was made of ileum and in the remainder it was made from the ileocaecal segment. In several patients additional surgical procedures were performed. In addition to the 2 men undergoing cystoprostatectomy, 6 patients underwent placement of an artificial urinary sphincter, 2 underwent colposuspension and 3 underwent simultaneous nephroureterectomy for a non-functioning kidney. Consideration was given to fitting an artificial urinary sphincter or to performing colposuspension in patients who had stress incontinence, and in those who had low compliance with leakage of urine at relatively low end-filling pressures (30–40 cm H_2O) on cystometrography (CMG).

Table 1 Indications for Operation

Spina bifida	16
Spinal neoplasm	2
Spinal trauma	1
Interstitial cystitis	2
Tuberculosis	2
Transitional cell carcinoma	2

Clinical assessment and follow-up

Before operation and at follow-up, particular note was made of symptoms of voiding dysfunction, the method and frequency of voiding, urinary continence, metabolic and renal function. Reviews were undertaken at regular intervals and to facilitate this a special clinic was established. Continence was graded according to degree of interference with lifestyle and we recorded the number of incontinence pads used per day. In addition, patients were asked to record their views on the final symptomatic outcome graded on a 5-point scale (ranging from worse to excellent).

The majority of patients had undergone preoperative conventional urodynamic study (CMG; n=23) and 16 had also undergone pre-operative ambulatory monitoring (AM). All patients underwent CMG and AM at a minimum of 3 months after operation. All were trained in the use of clean intermittent self-catheterisation (CISC) before operation.

Conventional urodynamic study

An initial assessment of free urinary flow rate and residual urine volume was made if the patients were voiding *per urethram*. Under local anaesthesia, 6 F and 10 F catheters were placed in the bladder. One was used to record bladder pressure, the other to fill the bladder. Standard filling rates of 50 and 100 ml/min were used, although many of the patients were also filled at 20 ml/min if found to have very small or extremely hyperreflexic bladders. Particular note was taken of the pressure rise on filling, sensation of filling, the presence of phasic bladder activity and the maximum cystometric capacity. Video screening was used to assess urinary continence. Patients were allowed to void by their usual method, whether by straining or by clean intermittent self-catheterisation. The terms and definitions of the International Continence Society (ICS) were used throughout unless otherwise stated (Abrams *et al.*, 1988).

Ambulatory monitoring

This was undertaken using purpose-built monitoring equipment as described previously (Griffiths *et al.*, 1989; Webb *et al.*, 1989). Bladder and rectal pressures were measured via solid-state Gaeltec transducers and the data stored digitally at a sampling rate of 1 Hz in solid state memory on a portable monitoring box. Incontinence was measured by an electronic nappy, the data again being recorded on the portable equipment. This was subsequently decoded and plotted for analysis. The patients were asked to void before the lines were placed and to undertake their normal pattern and frequency of voiding, whether by regular CISC or by normal voiding. Voided volumes and residual volumes were estimated during the course of the procedure. After an initial period of rest, patients were encouraged to drink and remain mobile to simulate their normal daily activities.

After operation, patients using CISC performed this technique during the course of AM by their normal method—either by regular timed intervals or by waiting for a sensation they associated with a full bladder.

Operative details

Bowel preparation was performed using a balanced electrolyte solution, "Golitely" (Thomas *et al.*, 1982). All patients underwent either ileocystoplasty or ileocaecocystoplasty. The latter procedure was based on that described by the Mainz group (Thuroff *et al.*, 1985), but only a single length of ileum was sutured in the opened out caecum and ascending colon. Systemic antibiotic prophylaxis (ampicillin, gentamicin, metronidazole) was administered pre-operatively and for a period of 24 h afterwards. In those undergoing cystectomy for transitional cell carcinoma a standard radical cystoprostatectomy was employed. In patients with a grossly thickened bladder at operation or in those with a very small bladder capacity, a supratrigonal cystectomy with excision of redundant bladder tissue was undertaken. The 2 patients undergoing revision of previous caecocystoplasty had the previous anastomosis taken down and a detubularised ileal patch interposed.

In general, the ileocaecal segment was used, but if the caecum was insufficiently mobile then a suitable length of preterminal ileum was used. The prepared bowel was isolated on its vascular pedicle and detubularised by opening along the antimesenteric border. The caecum and ascending colon were opened along the anterior taenia coli and the ileocaecal valve divided. Particular care was taken to diathermise bleeding vessels on the divided edge of the bowel and the detubularised segments were reconstituted using a single layer of continuous 4/0 PDS suture. The bowel anastomosis was performed with a single layer of interrupted 4/0 PDS sutures and the gap in the mesentery was closed. If ureteric reimplantation was required, it was performed by means of a Camey type implantation (Le Duc *et al.*, 1987). In each case a suprapubic tube with multiple fenestration was placed and a urethral catheter was inserted. Slow irrigation of the bladder with normal saline was carried out overnight with the pressure head limited to 30 cm H_2O. The catheters were irrigated daily with 50 ml of normal saline to clear any mucus and they remained *in situ* until the fourteenth day after operation, when a careful cystogram was performed. If this was satisfactory the urethral catheter was removed, but the suprapubic catheter was left *in situ* for a further 2 or 3 weeks.

Statistical analysis

Grouped data are reported as means ± 1 SD, but statistical analysis was carried out by means of tests suitable for non-parametrically distributed data including the Mann-Whitney test and the X^2 test with Yates' correction.

Results

Complications

No patient died after operation. One developed a clinically evident urinary leak which resolved after a further 10 days' catheter drainage and 2 patients were observed to have a small asymptomatic leak on the post-operative cystogram. These were treated with a further period of drainage and all healed uneventfully. One patient developed a left calf vein deep venous thrombosis on the ninth post-operative day which required anticoagulation, whilst another patient developed right-sided abdominal pain and fever on the tenth post-operative day. The only positive finding in this patient was of debris in the gallbladder and he settled on conservative management with antibiotics. Two patients early in the series had heavy haematuria which required several bladder washouts and transfusion: this point emphasises the need for careful haemostasis of the cut edge of the detubularised bowel segment. Two patients with spina bifida who have ventriculoperitoneal shunts for congenital hydrocephalus suffered symptoms of obstruction in the immediate post-operative period. Both underwent neurosurgical review but required no further management. We assume the problem to have arisen because of fibrin occluding the peritoneal end of the shunt tubing. Both patients have now made a full recovery.

Late complications included one patient with several episodes of severe epididimoorchitis which were treated with antibiotics and finally resolved. Another 70-year-old man required admission to hospital with suprapubic pain and fever 3 months after operation. Radiological investigation and biopsy confirmed osteitis of the pubis, which responded to intravenous antibiotic therapy. A 72-year-old lady was admitted to her local hospital 2 years after augmentation with adhesive intestinal obstruction that required a laparotomy. Finally, one young man required 2 revisions of his artificial urinary sphincter because of suspected kinked connector tubing. He eventually required insertion of a new control pump.

Pre-operative urodynamic findings on CMG (Table 2)

The pre-operative urodynamic findings are summarized in Table 2. In brief, most of the patients had bladders of small cystometric capacity and low compliance before operation, often accompanied by detrusor hyper-reflexia; 17 of 23 patients (74%) before operation were shown to be grossly hyperreflexic with mean pressures of 71 ± 38 cm H_2O (range 15–120 cm H_2O) on CMG; 13 of 22 patients (59%) before operation were incontinent during CMG. Of these, 5 (23%) demonstrated urge incontinence only, 5 demonstrated genuine stress incontinence and 3 (14%) had a combination of stress and urge incontinence during the investigation.

Post-operative urodynamic findings on CMG (Table 2)

The most striking findings were in relation to bladder capacity. Total bladder capacity (residual urine + filling volume) increased after operation from a mean of 122 ± 91 to 659 ± 431 ml ($P < 0.0001$) (Fig. 1). Cystometric bladder capacity also increased significantly from 101 ± 61 to 579 ± 391 ml ($P < 0.001$). Bladder compliance also improved significantly. The pressure rise on filling with CMG decreased from 23 ± 23 cm H_2O before operation to 7 ± 8 cm H_2O after operation ($P < 0.005$) (Fig. 2) and compliance (dV/dP) was found to increase from 25 ± 48 ml/cm H_2O to 277 ± 480 ml/cm H_2O ($P < 0.001$). After operation only 2 patients (9%) ($P < 0.005$) were shown to have hyper-reflexia measurable on conventional urodynamics (mean pressure 43 ± 23 cm H_2O). However, a further 3 patients had hyper-reflexia demonstrated on AM.

Ambulatory monitoring before and after operation

Voided volumes were measured during ambulatory monitoring, although before operation those patients with urinary diversion and severe urge incontinence could not be assessed. A significant increase from 153 ± 133 to 361 ± 231 ml ($P < 0.016$) was found after operation (Table 2). Hyper-reflexia was present in 14 of 16 patients (88%) studied preoperatively with amplitudes ranging from 15 to 160 cm H_2O (mean 54 ± 37). After operation, 3 patients (14%) had hyper-reflexia, and in these patients the amplitude was lower, ranging from 15 to 40 cm H_2O (mean 25 ± 13).

Before operation, 9 of 16 patients (56%) were incontinent during ambulatory monitoring; all but one of these were shown to have urge incontinence, whilst 2 exhibited stress incontinence during the study. After operation, 3 patients (17%) were found to have minor degrees of incontinence during ambulatory monitoring, 2 had urge incontinence associated with phasic peristaltic activity from the bowel segment and 1 had minor degrees of stress incontinence. Another patient had major stress incontinence, but he has since been fitted with a bladder neck sphincter and is now dry.

Phasic activity due to bowel activity

After operation, we observed the presence of regular

Table 2 Urodynamic Findings

	Investigation	*Pre-op*	*Post-op*
Total bladder capacity (ml)	CMG	122 ± 91	659 ± 431
Pressure rise on filling (cm H_2O)	CMG	23 ± 23	7 ± 8
Compliance (dV/dP) (ml/cm H_2O)	CMG	25 ± 48	277 ± 480
Voided volumes (ml)	AM	153 ± 133	361 ± 231

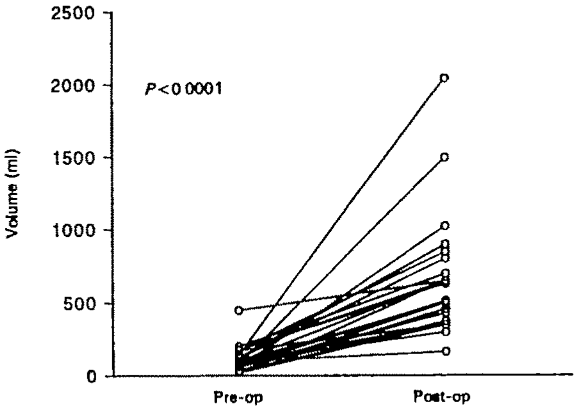

Fig. 1 Total bladder capacity (residual + filling capacity) before and after augmentation or substitution cystoplasty as measured on CMG.

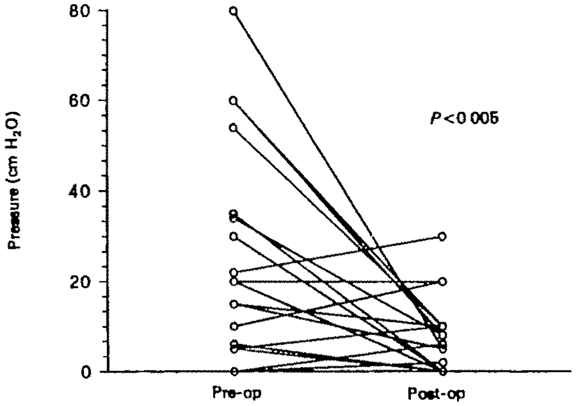

Fig. 2 Pressure rise on filling during CMG before and after augmentation or substitution cystoplasty.

phasic activity on both CMG and ambulatory monitoring which developed and increased in severity with filling. This was different in appearance from hyper-reflexia, being distinguishable by its well defined onset with filling at moderate volumes, its regular cyclical nature and uniform amplitude once established. Furthermore, we occasionally noted an apparent change in compliance at its onset, suggesting filling and distension of the bowel reservoir (Fig. 3). This pattern of "volume-dependent" regular phasic activity has been described by Light and Engelmann (1985) and is believed to be due to peristaltic activity occurring in the distended bowel segment. However, on occasion the distinction between phasic activity and hyper-reflexia was difficult and in these circumstances doubtful cases were classified as hyper-reflexia. Two patients exhibited phasic activity on CMG before operation and one of these was confirmed on ambulatory study. These pressures were of 30 cm H_2O and 40 cm H_2O at frequencies of 180 and 30 cycles/h respectively. Both patients had undergone previous cystoplasty and both complained of persistent urge incontinence.

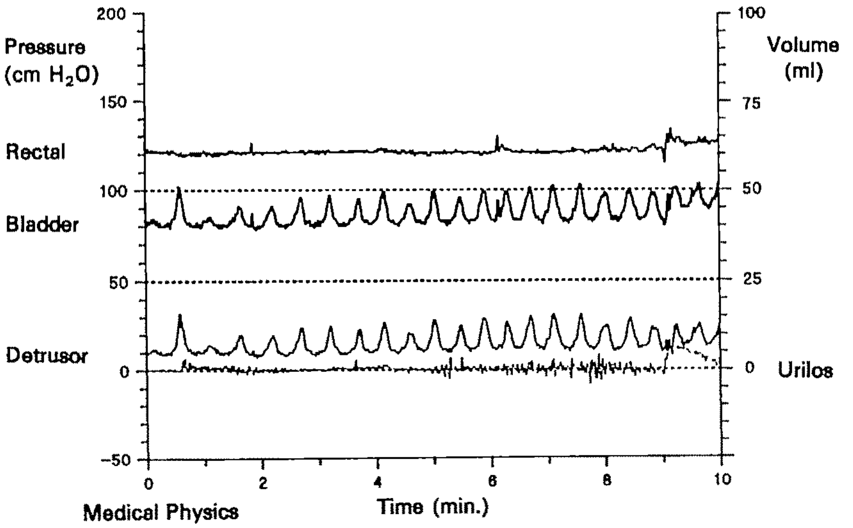

Fig. 3 Bowel-dependent regular phasic activity occurring during an ambulatory monitoring study, associated with deterioration in compliance and incontinence.

After operation, regular phasic activity was demonstrable in 11 of 22 patients (50%) on CMG. This was mostly of low amplitude (mean 21 ± 14 cm H_2O; range 5–50) with a frequency range of 20 to 360 cycles/h and was seen only in patients who had undergone ileocaecocystoplasty. The 2 patients who had undergone ileal augmentation of previous cystoplasties still had evidence of persistent regular phasic activity, although this was of much lower amplitude than before operation (5 and 10 cm H_2O respectively). These pressure waves gave rise to symptoms of urgency and frequency in 4 patients after operation. CMG did not detect this type of activity in patients who had undergone ileal cystoplasty alone.

Ambulatory monitoring demonstrated regular phasic activity in 10 patients (43%) after operation. Again, this was of low pressure (mean 24 ± 12 cm H_2O) and included 3 patients who had undergone ileal cystoplasty. These patients had regular asymptomatic phasic activity with an amplitude of about 20 cm H_2O.

Clinical outcome

The clinical outcome was good. In all, 23 patients (92%) were satisfied with the operation, 10 (40%) claiming it to have been a complete success. Only 2 patients were dissatisfied: one of these was suffering from marked stress incontinence and has since had a bladder neck artifical urinary sphincter fitted. He is now dry and happy. In retrospect, it is clear that he should have been fitted with a sphincter at the time of his augmentation, although on review of his pre-operative urodynamics he only had leakage observed on CMG at high end-filling detrusor pressure (45 cm H_2O). The other patient is unhappy using CISC, but on clinical grounds, with regard to continence and on urodynamic investigation, his operation appears to have been successful.

Eighteen patients (72%) rely on regular CISC for voiding and with the above exception find no difficulty with the technique. All describe a sensation of bladder filling, most of them reporting a sensation of "fullness". Indeed, several patients rely on this as a guide to their timing for CISC.

Only the one patient mentioned above had severe persistent incontinence after operation. However, a further 10 patients did admit to occasional symptoms of minor episodes of incontinence, although this was confirmed on urodynamic testing in only 3 patients, and the patients found these episodes to be infrequent and usually characterised by leakage of small amounts of urine at extremes of bladder filling. Some of these patients would use an occasional incontinence pad for insurance purposes. Four patients had symptoms of stress leakage alone, 5 complained of occasional urge incontinence or enuresis alone and 1 had mild symptoms of both stress and urge incontinence. As can be seen in Tables 3 and 4, these symptoms were not associated significantly with the presence of persistent hyper-reflexia or bowel-dependent phasic activity after operation.

Table 3 Post-operative Hyper-reflexia, Bowel-dependent Phasic Activity and Incontinence Assessed by CMG and AM

Incontinence (Urge+enuresis)	*Hyper-reflexia*		*Phasic activity*	
	Yes	*No*	*Yes*	*No*
Continent	4	12	13	3
Incontinent	1	5	4	2

All patients described production of mucus, 29% claiming an excessive amount. However, no patient described it as a particular difficulty or found that it interfered with his/her voiding technique.

Discussion

The principal objective in undertaking bladder replacement, or in augmenting the bladder with an extremely reduced capacity, must be to provide a reservoir which has adequate capacity, high com-

Table 4 Post-operative Hyper-reflexia, Bowel-dependent Phasic Activity Accessed by CMG and AM and Symptoms of Incontinence with Reference to Bowel Segment used

	Hyper-reflexia		*Phasic activity*		*Urge incontinence/enuresis*	
	Yes	*No*	*Yes*	*No*	*Yes*	*No*
Ileal	0	5	3	2	1	4
Ileocaecal	5	12	14	3	5	12

pliance with low filling pressures and hence to protect the upper urinary tract from dilatation and chronic damage. However, it is also vitally important that the neo-bladder retains continence yet is able to be emptied efficiently and easily by the patient, thus preventing the complications of stasis and infection, and maintaining the patient's independence.

Although bowel substitution has been used for many years, it is only relatively recently that the development and use of the artificial urinary sphincter has provided continence and hence the possibilities of augmentation and undiversion to the neuropathic patient. Careful use of CISC enables convenient and adequate emptying (Webb *et al.*, 1990). The choice of bowel segment and surgical technique in fashioning the augmentation has seen many variations. Many large series have been reported (Kuss *et al.*, 1970; Dounis *et al.*, 1980; Whitmore and Gittes, 1983; Goldwasser and Webster, 1986; Taguchi, 1987). The use of closed or tubularised segments appears to be complicated by the often high intraluminal pressures generated by peristalsis, and these appear to be higher on filling. Kock (1969) showed that closed loop segments of either the large or small bowel can generate pressures of up to 100 cm H_2O and detailed documentation of the type of pressure activity observed in ileal conduits has been reported previously (Neal, 1989).

Light and Engelman (1985) presented the results of urodynamic studies on 14 patients with various clinical problems who were undergoing lower urinary tract reconstruction with ileal, ileocaecal, ileocaecocolonic and sigmoid bowel segments. They observed pressure contractions (maximum 90 cm H_2O) in the ileocaecal segment used for bladder augmentation. However, of 3 patients who had undergone cystoplasty with ileal segments alone, only 1 had low amplitude contractions (<48 cm H_2O). In general, our results confirm these findings, although the pressures we observed in the detubularised ileocaecal segment were of lower pressure (21 ± 14 cm H_2O). We only detected activity in patients with ileal segments alone by means of ambulatory monitoring, and this was of very low pressure (20 cm H_2O).

The main finding of this study is that bladder augmentation with detubularised ileal or ileocaecal bowel segments has a very satisfactory clinical outcome in selected patients. We have also shown that after augmentation, phasic pressure activity owing to the function of the bowel segment can lead to significant urinary symptoms, but such pressure activity was of much lower amplitude in patients undergoing augmentation with only ileum. This should be taken into consideration when replacing the bladder after cystectomy, when sphincter function is impaired, and when considering the need for long-term prevention of upper urinary tract damage. However, the significant increases in functional and total bladder capacity combined with the finding of low pressure filling and high compliance when either ileum or the ileocaecal segment was used confirm their suitability for most patients.

The majority of patients rely on CISC for voiding, although the remaining patients manage adequately using natural or straining voiding techniques. This reliance on the use of self-catheterisation in patients undergoing bladder reconstruction has also been emphasised by a study of patients undergoing ileocystoplasty for idiopathic detrusor instability (Sethia *et al.*, 1991).

All patients are kept under continual review with regard to renal and metabolic function (Nurse *et al.*, 1988; Nurse and Mundy, 1989a) and so far there have been no significant clinical difficulties. In view of the possible risk of malignacy in the bowel segment (Kirby and Lloyd-Davies, 1985; Stone *et al.*, 1987; Nurse *et al.*, 1989b), we have begun a programme of regular cystoscopy for these patients, although it is likely to be several years before any of them will be at risk of this problem. The clinical outcome of bladder augmentation and replacement has been good and the high degree of patient satisfaction indicates that such procedures are useful and safe provided that patients are selected and followed up carefully.

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The Neurourology of Tropical Spastic Paraparesis

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Summary—We report the clinical features, urodynamic results and neurophysiological findings in 6 patients with urinary symptoms related to tropical spastic paraplegia. The widespread nature of the pathological changes within the nervous system result in a complex variety of urodynamic and neurophysiological features.

Tropical spastic paraparesis (TSP) is a condition associated with and probably caused by the retrovirus human T-cell lymphotropic virus type 1 (HTLV-1) (Gessain *et al.*, 1985; Cruickshank *et al.*, 1989). It is a common cause of paraparesis in the West Indies (Montgomery *et al.*, 1964) (where it was formerly known as Jamaican neuropathy or myelopathy) and in the southern islands of Japan (Osame *et al.*, 1987) (where it is called HTLV-1 associated myelopathy or HAM), but it is also found widely in the tropics and sub-tropics (Roman *et al.*, 1985) and in immigrants to northern Europe from endemic areas (Newton *et al.*, 1987; Cruickshank *et al.*, 1989; Gout *et al.*, 1989). The condition is characterised by a progressive paraparesis associated with back pain and micturition disturbances. Pathologically there is a meningomyelitis with demyelination and axonal loss, particularly affecting the corticospinal tracts. These findings are most marked in the low thoracic and upper lumbar regions (Montgomery *et al.*, 1964; Cruickshank *et al.*, 1989; Iwasaki, 1990).

While there have been many reports concerning the clinical and immunological features of this condition, little attention has been paid to the bladder dysfunction which commonly accompanies it. The only previous study concerned Japanese patients, most of whom had urodynamic evidence of detrusor hyper-reflexia and detrusor sphincter dyssynergia (Shibasaki *et al.*, 1988). We report the urodynamic and neurophysiological findings in a small group of Caribbean immigrants to the United Kingdom.

Patients and Methods

Six patients of West Indian origin were studied. All had tropical spastic paraparesis with antibodies to the human T-cell lymphotropic virus type 1 in their serum and cerebrospinal fluid, and all had evidence of the integrated virus in their leucocytes when assessed by the polymerase chain reaction.

Urodynamic studies

Standard urodynamic studies were performed. The patient was asked to void, and then the bladder was filled with saline at a rate of 30 ml/min. Throughout the study the bladder and rectal pressures were measured, allowing a detrusor pressure to be calculated. When the bladder was full, the filling catheter was removed and the patient was asked to void. The procedure was repeated at least once to ensure reproducibility, and the mean values for each patient are quoted. The final residual volume was then measured. Synchronous pelvic floor electromyography (EMG) was performed using either an anal plug electrode or a needle inserted in the anal sphincter.

Neurophysiological studies

(i) Urethral sphincter EMG with motor unit analysis. This was performed as described by Fowler *et al.* (1984). A concentric needle electrode was inserted

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into the striated urethral sphincter and individual motor units were identified, using a delay line and signal triggering. The duration and amplitude of each motor unit was measured and in addition the number of phase reversals of more than 0.1 mV were counted. A motor unit was considered to be polyphasic if there were more than 5 such "turns".

In each patient, 8 to 10 motor units were isolated and analysed and the mean motor unit duration and amplitude were calculated. In addition, the total number of polyphasic motor units was noted.

(ii) Sacral reflex latency. With the concentric needle electrode *in situ*, the sacral reflex latency was then measured. The stimulus was provided by 2 saline soaked electrodes, 2 cm apart, which were applied to the dorsum of the base of the penis or clitoris in the midline, with the anode most proximal. Square-wave stimuli of duration 0.1 ms were applied at a frequency of 1 Hz. The stimulus was further increased until an EMG response was recorded in the urethral sphincter or until the stimulus became too strong for the patient to tolerate. Ten responses were recorded for each patient and the shortest latency between stimulus and EMG response was recorded.

(iii) Pudendal somatosensory evoked potential. The cortical somatosensory evoked potential was recorded as described by Opsomer *et al.* (1986). Two silver disc electrodes were attached to the scalp, with the recording electrode placed 2 cm behind the vertex (in the Cz-2 position) and the reference electrode attached on the forehead (in the Fz position) (Jasper, 1958).

A square wave stimulus of 0.1 ms duration was applied to the dorsal nerve of the penis or clitoris, as described above, at a frequency of 2 Hz. The stimulus intensity was usually 2 to 3 times the sensory threshold. Using a signal trigger and averaging technique, the response to a minimum of 128 stimuli was amplified and displayed on the recorder. If a clear response was not seen at this time, stimulation was continued until a maximum of 256 stimuli had been applied. The procedure was repeated at least once to ensure reproducibility and the average latency of the first negative deflection (the P1 response) was recorded.

(iv) Motor evoked potential. The motor evoked potential of the striated urethral sphincter to magnetic stimulation of the brain was recorded using the technique described by Eardley *et al.* (1990).

For cortical stimulation, a stimulating coil was held with its centre 2 to 4 cm behind the vertex. The stimulus intensity was increased until an EMG response was recorded in the urethral sphincter, or until the maximum output of the stimulator was reached. The concentric needle electrode in the urethral sphincter recorded the EMG response to stimulation via a trigger mechanism. Each recording was repeated at least 3 times to ensure reproducibility and the shortest latency was recorded in each case. Responses were recorded initially with the patient relaxed, and then while the patient voluntarily contracted his or her sphincter to obtain a "facilitated" response.

The spinal nerve roots were stimulated using a similar technique.

Results

Clinical features

Demographic details of the patients are given in Table 1. All had typical neurological findings of TSP with a spastic paraparesis associated with a variable amount of sensory loss in the lower limbs.

Five of 6 patients had irritative urinary symptoms (frequency, nocturia or urgency) and in all but 1 there was associated urge incontinence. Three

Table 1 Details of Patients

Patient	*Sex*	*Age (years)*	*Duration of disease (years)*	*Duration of urinary symptoms (years)*	*Urinary symptoms*
L.S.	F	54	3	2	Hesitancy, poor stream, urgency
D B.	F	34	5	5	Urinary retention
L.N.	F	65	11	5	Frequency, urgency, urge incontinence
F S	F	70	5	4	Frequency, urgency, urge incontinence
C.G.	M	61	2	2	Frequency, urgency, urge incontinence, poor urinary stream
E J	F	54	17	6	Frequency, urgency, urge incontinence

patients had obstructive symptoms (hesitancy, poor stream or incomplete bladder emptying) and in 1 patient this had been associated with episodes of urinary retention. In all cases the urine was sterile.

Urodynamic studies

A summary of the urodynamic results is give in Table 2. Four patients had large residual volumes, both at the beginning and at the end of the study. One of these was the patient who had previously developed urinary retention and she had been catheterised immediately prior to the study. Three patients had detrusor hyper-reflexia and all were incontinent during the test. Two patients had evidence of detrusor areflexia; both voided largely by abdominal straining with peak detrusor pressures of 12 and 5 cm of water. One elderly diabetic male patient had the urodynamic characteristics of bladder outflow obstruction, which could have been due to prostatic disease.

Synchronous urethral sphincter EMG during urodynamics was technically unsatisfactory in all but 2 patients. In one (D.B.) the sphincter relaxed slowly but completely, and in the other (F.N.) there was evidence of detrusor-external sphincter dyssynergia.

Neurophysiological studies (Table 3)

(i) Urethral sphincter EMG. Six patients underwent urethral sphincter EMG. Grade III complex repetitive discharge and decelerating bursts (Fowler *et al.*, 1985) were heard in 2, but this did not prevent motor unit analysis.

In 2 patients (D.B., E.J.) there was evidence of denervation and reinnervation in the striated urethral sphincter, with prolonged motor unit duration (Fig. 1); the motor units were normal in the other patients. Eleven polyphasic motor units were found, all in multiparous females.

(ii) Sacral reflex latency. Of the 5 patients studied, none of the women had a measurable response, but the reflex was normal in the male patient.

(iii) Somatosensory evoked potential. Of the 5 patients studied, 2 had abnormal responses. In one (D.B.) the response was absent and in the other (C.G.) the response was delayed (Fig. 2).

(iv) Motor evoked potential. All 4 patients studied had abnormal responses to cortical stimulation; in 2 the response even with facilitation was absent and in 2 it was delayed (Fig. 3).

Discussion

Two patterns of abnormality emerge in this small study. Two of the patients had atonic bladders and

Table 2 Urodynamic Results

Patient	*Residual urine volume (ml)*	*Bladder capacity (ml)*	*End-fill pressure (cm H_2O)*	*Filling trace*	*Peak flow rate (ml/s)*	*Voiding pressure (cm H_2O)*	*Residual urinary volume (ml)*
L.S.	250	800	12	Stable	10	12	600
D.B	*	680	4	Stable	0	5	680
L N	0	520	22	Hyper-reflexia	34	35	0
F S.	175	525	35	Hyper-reflexia	12	15	150
C.G.	150	505	20	Stable	4	105	245
E.J.	0	220	46	Hyper-reflexia	16	42	20

* This patient had been previously catheterised to treat an episode of acute urinary retention.

Table 3 Neurophysiological Studies

Patient	*Detrusor pattern*	*Synchronous sphincter EMG*	*Motor unit analysis*	*Somatosensory evoked potential*	*Motor evoked potential*
L.S.	Areflexia	—	Normal	Normal	Delayed
D.B.	Areflexia	Slow relaxation	Denervation	Absent	Absent
L.N.	Hyper-reflexia	Dyssynergia	—	—	—
F.S.	Hyper-reflexia	—	Normal	Normal	Delayed
C.G.	Stable	—	Normal	Normal	—
E.J.	Hyper-reflexia	—	Denervation	Delayed	Absent

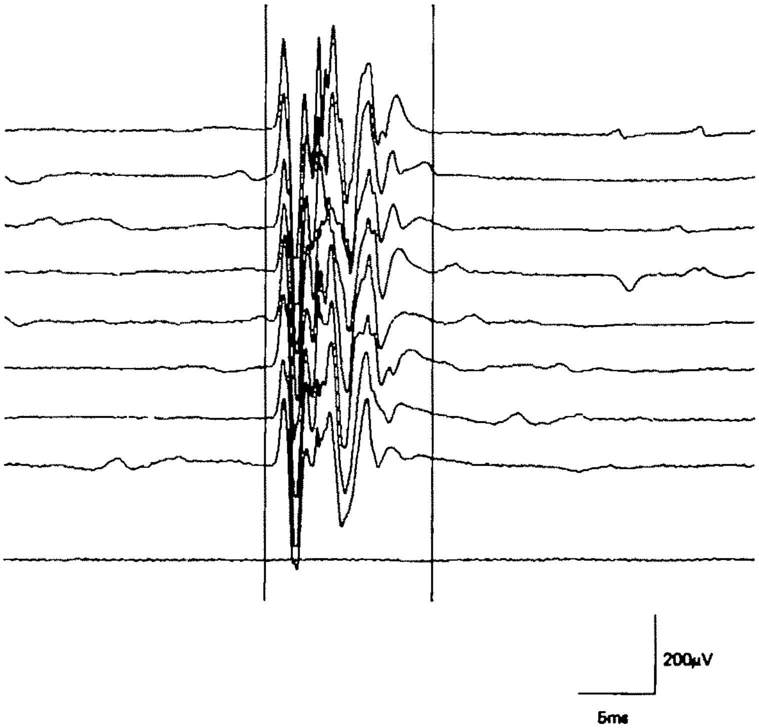

Fig. 1 Repeatedly firing, prolonged, polyphasic motor unit recorded in a female patient with tropical spastic paraparesis

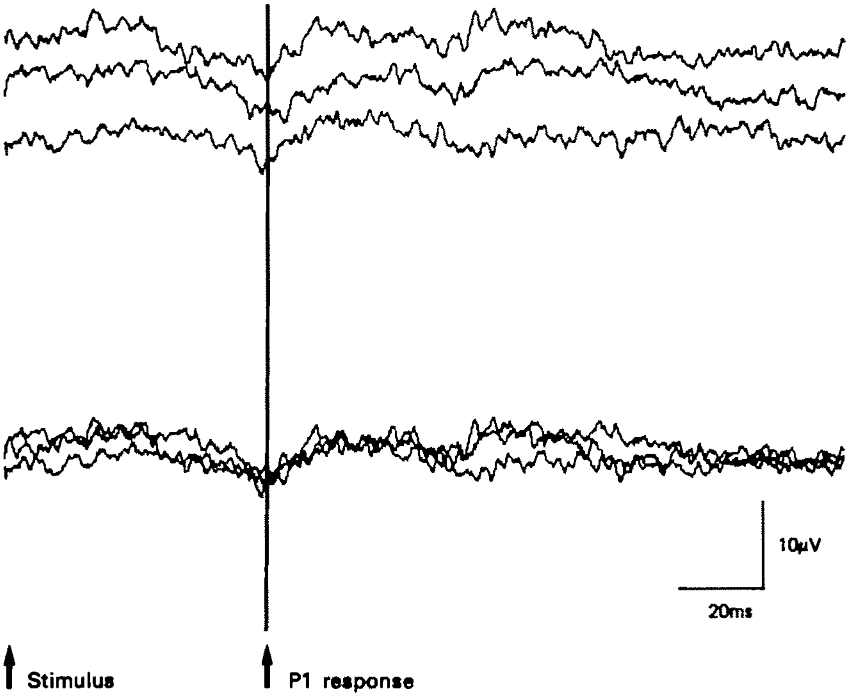

Fig. 2 Delayed pudendal somatosensory evoked potential. Three separate recordings have been made and the lower tracing comprises the upper 3 tracings, superimposed on each other

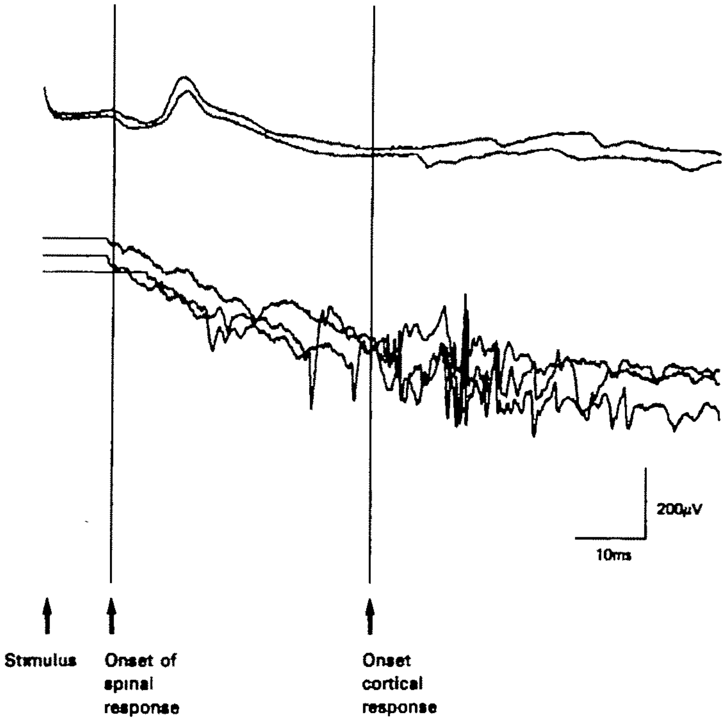

Fig. 3 Delayed motor evoked potential from a patient with tropical spastic paraparesis The upper traces are the responses to spinal stimulation (which are within the normal range) and the lower responses are delayed responses to cortical stimulation. This indicates delayed motor conduction within the central nervous system

3 had detrusor hyper-reflexia. One elderly diabetic male patient had evidence of bladder outflow obstruction.

Atonic bladders are generally associated with lesions of the peripheral innervation of the bladder. In tropical spastic paraparesis there is pathological evidence of posterior and anterior nerve roots being entangled in inflammatory exudate, which might account for this urodynamic finding. Furthermore, it is known clinically that a proportion of patients have evidence of denervation in the lower limbs (Arimura *et al.*, 1987) and pathological studies from Japan (Iwasaki, 1990) show that Onuf's nucleus may also be involved in tropical spastic paraparesis. This might account for the findings of denervation and reinnervation seen in some patients.

Detrusor hyper-reflexia is typically associated with damage to the suprasacral central nervous system. The descending tracts to the bladder are probably situated equatorially in the lateral columns (Nathan and Smith, 1958). Pathologically there is commonly equatorial demyelination, at least in the material obtained by Montgomery *et al.* in 1964, which has been reviewed by one of the present authors (P.R.). Such damage would be an adequate explanation of the hyper-reflexic bladder problems of these patients. More proximal lesions in the brain stem or cerebrum are unlikely to be the cause of these problems, particularly as there are only minor pathological changes in these sites, usually taking the form of perivascular infiltration rather than foci of demyelination or axonal destruction. The abnormalities of central motor conduction are consistent with this hypothesis, although it is important to note that cortical stimulation assesses conduction within the corticospinal tract. To what extent sensory information carried in the dorsal columns is involved in bladder dysfunction is unknown, but it is noteworthy that the somatosensory evoked potentials were normal in 3 of the 5 patients studied.

In summary, bladder disturbance in TSP is complex; it can cause a lower motor neurone or an upper motor neurone dysfunction, consistent with damage either to the sacral outflow to the bladder or to the descending tracts to the sacral nuclei.

Acknowledgement

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Experience with the Intraprostatic Spiral

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Summary—Thirty-six patients have been followed up after insertion of an indwelling intraurethral device for prostatic obstruction. Follow-up exceeded 1 year in some cases. The main problem was dislocation of the spiral not only in the early stages but also after several months. Endoscopic assessment of the obstruction seems important during the pre-operative investigations. The ideal indication is prostatic obstruction in patients who are unsuitable for surgery and who need relief of acute retention for a limited time only. In selected patients the prostatic spiral has a place in the treatment of obstructive prostatism.

The conservative treatment of benign prostatic hypertrophy (BPH) has aroused renewed interest recently, although transurethral resection of the prostate (TURP) or adenomectomy remains the treatment of choice. Medical treatment and prostatic hyperthermia can be used in patients unwilling to undergo surgery. In patients with urinary retention who are unsuitable for surgery the only solution could be an indwelling catheter.

In 1978 Fabian developed a prostate spiral and later reviewed his results (Fabian, 1980, 1984). Since then, other authors have published reports on the same device (Flier and Seppelt, 1987; Vicente *et al.*, 1989; Chen *et al.*, 1990) or a similar one (Nordling *et al.*, 1989). The short-term results were quite good. More recently an alternative indwelling device has been developed (Nissenkorn, 1989).

In order to evaluate the role of an indwelling device in the treatment of inoperable patients with prostatic obstruction we studied a larger group of patients with a longer follow-up.

Patients and Methods

Between July 1988 and November 1989 we treated 36 patients with outflow obstruction by inserting a prostatic spiral (Prostakath) which is covered with a thin layer of gold; 34 of these patients had benign prostatic hypertrophy and 2 had prostatic cancer; 24 patients presented with urinary retention. TURP was not considered because of severe senile dementia in 7 cases, advanced age in 9, absolute contraindication to surgery in 11, the need for a temporary solution in 6 and the presence of concomitant malignancy in 3.

The prostatic spiral is inserted under local anaesthesia with ultrasonographic control. The bladder is filled with 200 to 300 ml of saline through a 21 F Tiemann catheter. A 6 F ureteric catheter is introduced into the bladder through the lateral opening of the Tiemann catheter, which is then withdrawn, leaving the ureteric catheter behind as a guide for insertion of the spiral. The length of the prostatic urethra is measured by suprapubic sagittal ultrasonography as the distance between the bladder neck and the apex of the prostate. Spiral length is calculated as the length of the prostatic urethra plus 15 mm in order to take into account the posterior curve of the urethra and to locate the proximal tip of the spiral inside the bladder. The spiral is inserted over the ureteric catheter with sonographic control (Figs 1 and 2). The insertion catheter and the ureteric catheter are then removed.

After the procedure the patients received antimicrobial treatment for 5 days and were evaluated after 3 weeks, 3, 6 and 12 months. Follow-up included subjective and objective assessment, including ultrasonography of the spiral and recording of residual urine, calcification and bacteriuria. When dislocation occurred the spiral was reposi-

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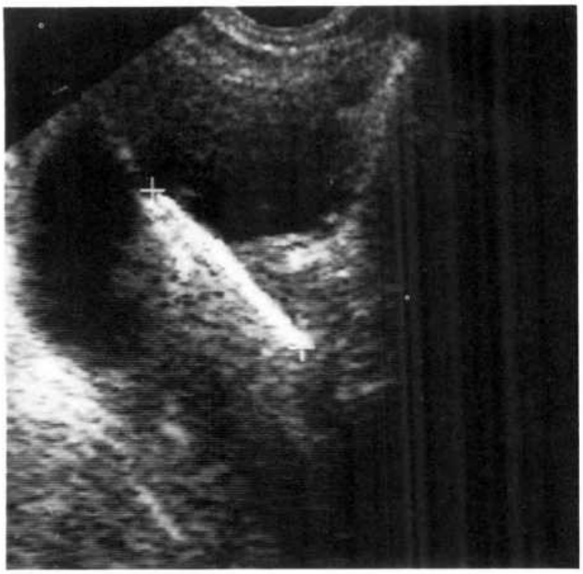

Fig. 1 Ultrasonography of correctly placed prostatic spiral, the tip reaching the half-full bladder.

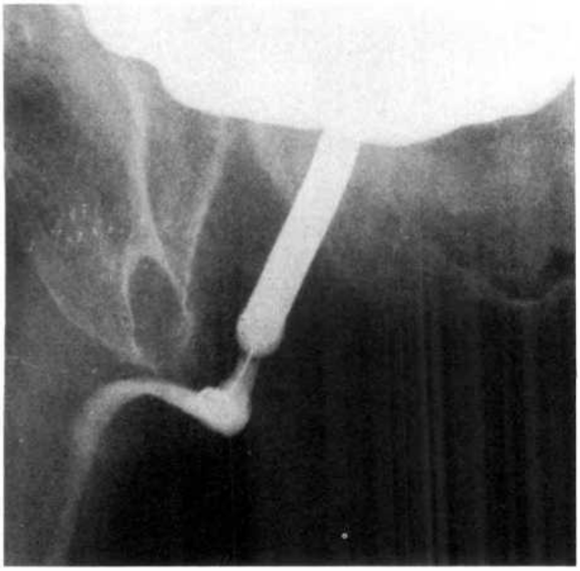

Fig. 2 Voiding urethrogram after placement of spiral.

tioned endoscopically: its distal end was grasped with foreign body forceps and it was repositioned under local anaesthesia. The result was classified as good when a normal voiding pattern and continence were established, with no residual urine and no bacteriuria. The outcome was classified as bad if the patient was unable to tolerate the device, or if there was incontinence, retention, stone formation or infection.

Results

Placement of the spiral caused no problems and the procedure was always well tolerated under urethral anaesthesia. Most patients were able to void spontaneously and could stop the urinary stream immediately after placement of the device. Assessment was difficult in the demented patients and also in a patient with chronic urinary retention where voiding was not spontaneous but provoked by suprapubic pressure.

Within 3 weeks 3 spirals were dislocated. One had to be removed following antegrade dislocation, when the patient insisted on withdrawal. Two patients had successful endoscopic repositioning. Twenty-six patients had normal micturition (72%); of the remaining 9 patients, 5 with severe irritative symptoms were treated with anticholinergic drugs. One patient was still unable to void due to bladder atony and was therefore drained suprapubically. In another patient the longest device available proved too short to cover a huge median lobe and he underwent a suprapubic prostatectomy. After 3 weeks 26 successes were recorded (72%), 3 complete failures (8%) and 7 partial failures (19%).

Of the initial 36 patients, 29 were evaluated after 3 months, but 4 have not yet reached that stage. As described above, 1 patient had a suprapubic indwelling catheter, 1 had a suprapubic prostatectomy and in the remaining patient the device was removed. Of these 29 patients, 24 had normal micturition. Four of them died between 3 and 6 months with well functioning spirals and 1 had a delayed TURP. In 5 patients the spiral was dislocated; 1 died, 2 underwent TURP and in the other 2 the spiral was removed. One of the latter group had severe encrustations that obliterated the spiral almost completely and caused obstruction (Fig. 3). This patient had a history of bladder stones and had undergone a cystolithotripsy at the time of spiral placement. After 3 months we recorded 5 failures; these, together with the initial 3 failures (within 3 weeks), yielded a complete failure rate of 8/32 (25%). In the remaining 24 patients the results were good.

Of the 29 patients evaluated after 3 months, only 17 could be evaluated after 6 months. Five of the remainder died, 2 have not yet been followed up for 6 months, 3 had a TURP, and in 2 cases the spiral was removed. All 17 patients had normal micturition, although 6 died between 6 and 12 months with well functioning spirals. After 6 months, therefore, the failure rate did not increase and success was documented in 17/22 patients (77%).

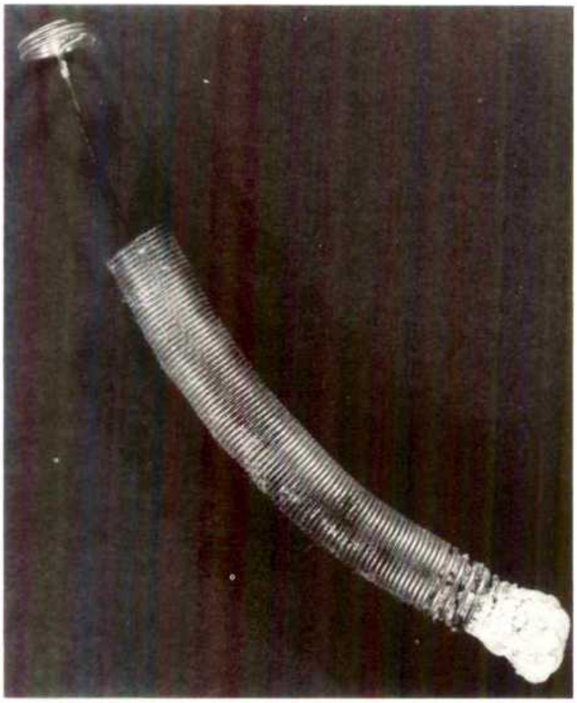

Fig. 3 Almost completely encrusted spiral which was evacuated spontaneously by a patient who had undergone simultaneous cystolithotripsy and insertion of the spiral.

Of the 17 patients evaluated after 6 months, only 10 could be evaluated after 12 months. This was because 6 patients died and 1 has not yet been followed up for 12 months. Of the remaining 10 patients, 4 presented with dislocation of the spiral; 2 were treated by TURP and the other 2 were untreated because they had no symptoms. The 6 other patients had normal micturition; the success rate after 12 months was therefore 60%.

To date, 4 patients have been followed up for 13, 15, 15 and 15 months respectively without problems.

Discussion

We encountered no difficulties when inserting the spiral under local anaesthesia and suprapubic echographic guidance was effective. More recently we have also checked the exact positioning with transrectal ultrasound, which provided excellent visualisation of the sphincter and the distal end of the spiral. Repositioning and withdrawal of the spiral under endoscopic vision proved easy when a rotating movement was superimposed on the antegrade or retrograde manoeuvre.

Early dislocation of the spiral probably implies that the procedure is unnecessary, since genuinely obstructive prostatic lobes keep the spiral in place. Stress incontinence is always a consequence of antegrade migration of the device. Urgency and urge incontinence occur, just as they do after relief of obstruction by TURP or adenomectomy (motor urge), or as a consequence of irritation (sensory urge). Anticholinergic and antispasmodic drugs are highly effective in these situations and the complaints also tend to disappear spontaneously after a few days (Fabian, 1984; Flier and Seppelt, 1987; Nordling *et al.*, 1989; Vicente *et al.*, 1989).

Late spiral dislocation is frequent and the aetiology is not clear. Our patients experienced both antegrade and retrograde dislocation in the twelfth month or even later. Not all previous reports have mentioned this problem (Fabian, 1984), but in more recent series it has been recorded in 25% of patients (Nordling *et al.*, 1989; Vicente *et al.*, 1989).

In early dislocation one can attempt repositioning but when dislocation recurs another approach should be adopted. For late dislocation it seems logical that repositioning would be successful, although we believe that removal and a "wait and see" policy can be adopted.

One patient presented with stone formation which filled the whole device. It should be noted, however, that when the spiral was inserted he had a bladder stone removed at the same time. We have not found any encrustation in the Prostakath spirals even when they had been in place for more than 1 year.

The best results were achieved in patients with acute urinary retention. The result was less good in patients with chronic urinary retention and decompensated bladders. The main advantage of the prostate spiral over the indwelling catheter is the resolution of bacteriuria (Fabian, 1984; Flier and Seppelt, 1987; Nordling *et al.*, 1989; Vicente *et al.*, 1989).

Our experience has shown that the prostate spiral is not a good solution for the enormous prostate, for irritative prostatism, for the chronically decompensated bladder and for long-standing obstruction. An enlarged middle lobe is also a relative contraindication (Chen *et al.*, 1990). We have not sufficient evidence to recommend its use as an alternative to an indwelling bladder catheter in demented patients, although patients who pull out their indwelling balloon catheters may be good candidates. Our experience in prostate cancer is small, although in both of our patients the goal of treatment was reached without complication or dislocation and continence was perfect. Advanced prostate cancer obstruction in the elderly can also be a relative indication (Roth and Rathert, 1988; Chen *et al.*, 1990).

The ideal indication for placement of an indwelling intraurethral device is obstructive benign prostate hypertrophy in inoperable patients who present with acute retention and need relief of obstruction for a limited period only (Nielsen, 1989). The prostatic obstruction should be assessed endoscopically to reduce the risk of subsequent or recurrent dislocation (Chen *et al.*, 1990).

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Peri-operative Blood Transfusion in Relation to Tumour Recurrence and Death after Surgery for Prostatic Cancer

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Summary—Several reports have suggested that peri-operative blood transfusion promotes tumour recurrence and death after surgery for cancer. We have studied the effect of transfusion in 156 patients operated on for prostatic cancer. A retrospective review was made of the clinical, histopathological and transfusion data in their hospital records. Sixty patients received blood transfusions and 96 did not. The 5-year prostatic cancer specific survival rate was 0.56 in the transfused patients and 0.69 in the non-transfused group. The transfused patients had a higher prevalence of risk factors than did the non-transfused. When the differences in risk factors were accounted for by Cox regression analysis, peri-operative blood transfusion reduced the prostatic cancer death intensity by 36%. The study does not support the hypothesis that blood transfusion promotes recurrence following surgery for prostatic cancer.

It has been suggested that peri-operative blood transfusion increases tumour recurrence and death after cancer surgery (Burrows and Tartter, 1982). The mechanism behind this phenomenon is not known, but it is believed to be the result of immunosuppression induced by some unknown substance in the transfused blood (Taylor and Parrott, 1982). It seems to be analogous with the finding that human kidney allografts have a better prognosis in the transfused recipient than in the non-transfused. The issue has been extensively studied in patients with colorectal cancer but only a few studies have addressed urological cancers. Two studies have failed to demonstrate any effect of blood transfusion on renal carcinoma (Manyonda *et al.*, 1986; Moffat *et al.*, 1987). A detrimental effect was claimed in 1 series that included a variety of tumours, among them prostate cancer (Blumberg *et al.*, 1986). In another study of patients with non-metastatic prostatic carcinoma, transfused patients had a significantly poorer recurrence-free survival than non-transfused patients (Heal *et al.*, 1988).

The aim of the present study was to test the hypothesis that peri-operative blood transfusion increases the prostatic cancer death rate after surgery for carcinoma of the prostate.

Patients and Methods

Between 1978 and 1986, 156 patients underwent first-time transurethral or transvesical prostatic surgery with a histological diagnosis of carcinoma of the prostate.

We reviewed the hospital records of these patients with regard to the clinical, surgical and histopathological data. The number and type of transfusions given peri-operatively (*i.e.* ±30 days from the day of operation) were also recorded. Most patients with prostatic cancer were seen regularly in the out-patient clinic, so that reliable follow-up data were available in most patients. In the remaining patients we obtained follow-up data from the records of other hospitals, from the Danish Cancer Register or from the Central Register of Deaths of the Danish National Health Service.

No consistent transfusion policy existed in

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Table 1 Type and Number of Transfusions in 60 Patients

	No. of units						*Total no of units*
	1	*2*	*3*	*4*	*5*	*>5*	
Whole blood	16	15	8	7	3	5	151
Packed blood	3	10	0	1	0	1	33
Washed erythrocytes	1	1	0	0	0	0	3
No of units transfused irrespective of type	15	16	10	7	5	7	187

Denmark at that time. Transfusions were given at the discretion of the surgeon or the anaesthetist.

The recorded data were stored on an IBM 30-021 desktop computer and analysed by dBase IV (R) and SOLO (R) statistical software. Groups of data were summarised by median, minimum and maximum values. Standard non-parametric tests were used.

Since many patients with prostatic cancer are elderly and die from other diseases, we concentrated on prostatic cancer specific survival (time measured from the day of operation to the day of death from prostatic cancer) rather than on overall survival (time measured from the day of operation to the day of death from any cause). Recurrence-free survival had to be abandoned as a survival parameter, since many patients deteriorated gradually, making the dating of a recurrence invalid in this retrospective study. The unadjusted survival rates were calculated from the Kaplan-Meier estimate and compared by the log-rank test (Peto *et al.*, 1977). Multiple regression by the Cox model was used to adjust for differences in prognostic variables (Cox, 1972).

Results

During the study period, 148 patients underwent transurethral resection and 8 had transvesical operations for prostatic carcinoma. Sixty patients (38%) were transfused and 96 (62%) were not. Table 1 shows the number of transfusions in relation to time and type of blood product; 27% of the units were given pre-operatively, 42% were given intra-operatively, and 31% were given after the day of operation; 48% of the transfused patients received more than 2 units, the maximum number being 11.

The clinical data suggest that patients receiving transfusions had more advanced disease than those who were not transfused (Table 2). In particular, the transfused patients had significantly larger tumours, lower pre- and post-operative haemoglobin values and poorer kidney function. They also had more locally advanced tumours and a higher frequency of metastatic disease. A higher proportion had subsequent orchiectomy, hormonal therapy or radiotherapy.

Table 2 Clinical Data in 156 Patients Operated for Prostatic Cancer according to Transfusion

	Non-transfused (n=96)	*Transfused (n=60)*	*P*
Age (years)	74 (56–89)	73 (55–93)	0.36*
Estimated weight of gland (g)	30 (20–50)	50 (30–80)	0.009*
Prostatic acid phosphatase (u/l)	5 (0–2030)	7 (0–314)	0.24*
Pre-operative haemoglobin (mmol/l)	9.0 (6.3–11.1)	8.1 (4.7–10.9)	0.000*
Pre-operative kidney function test			
Normal	78 (87.6%)	43 (76.8%)	0.05**
Abnormal	11 (14.4%)	13 (23.2%)	
Stage			
T0	40 (41.6%)	24 (40.0%)	
T1–T2	30 (31.3%)	17 (28.3%)	0.82**
T3–T4	26 (27.1%)	19 (31.7%)	
M0	63 (65.6%)	35 (58.3%)	0.36**
M1	33 (34.4%)	25 (41.7%)	
Type of operation			
Transvesical	1 (1.0%)	7 (11.7%)	0.003**
Transurethral	95 (99%)	53 (88.3%)	
Weight of operative specimen (g)	16 (4–40)	24 (10–70)	0.002*
Post-operative haemoglobin (mmol/l)	8.3 (6.0–11.1)	7.9 (6.0–10.1)	0.025*
Histopathological differentiation			
High	43 (45.3%)	24 (42.2%)	
Medium	37 (38.9%)	23 (40.2%)	0.48**
Low	15 (15.8%)	10 (17.6%)	

* Mann-Whitney test.
** χ^2 test.

At follow-up in 1988, 82% of the transfused

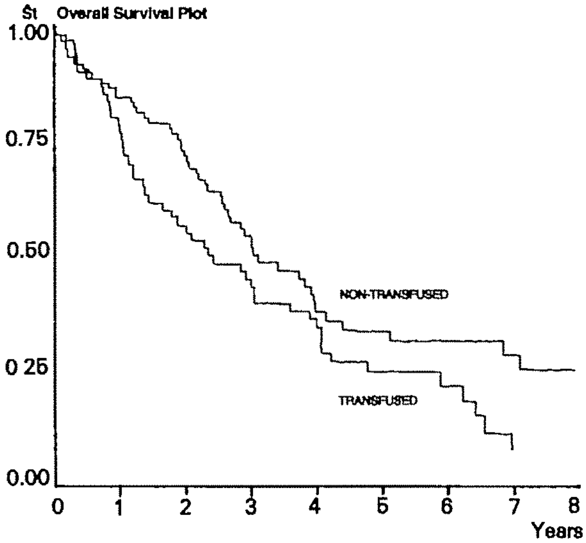

Fig. 1 Unadjusted overall survival in 156 patients operated on for prostatic cancer: 60 had been transfused, 96 had not.

patients had died, compared with 57% of the non-transfused patients ($P=0.001$). In the transfused group, 35.0% had died from prostatic cancer, compared with 22.9% in the non-transfused group ($P=0.14$). The 5-year overall survival rates were 0.25 and 0.32 respectively ($P=0.24$, log-rank test) (Fig. 1). The unadjusted prostatic cancer specific 5-year survival rates were 0.57 and 0.69 respectively ($P=0.44$, log-rank test) (Fig. 2).

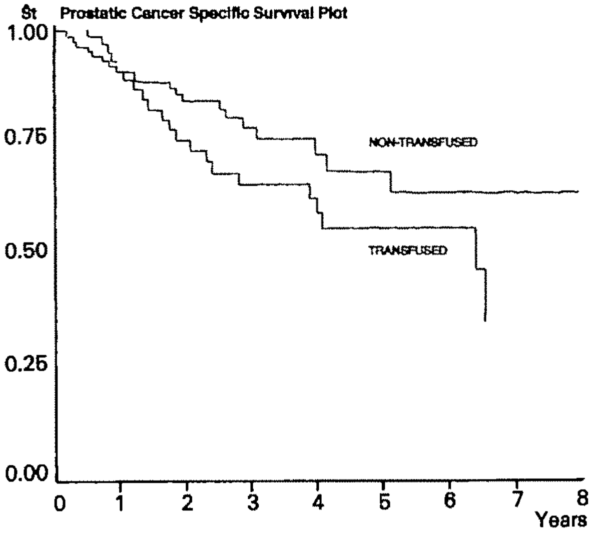

Fig. 2 Unadjusted prostatic cancer survival in 156 patients operated on for prostatic cancer: 60 had been transfused, 96 had not.

Table 3 Result of Cox Multiple Regression Analysis of Prostatic Cancer Specific Survival. (The scoring used in the model is given in parentheses)

	Regression coefficient	*SD*	χ^2	*P*
Primary model				
Age (<=70 years 0) (>70 years 1)	−0.422	0.341	1.53	0 216
T stage (<=T2: 0) (>T2: 1)	0.0453	0 345	0.02	0.895
M stage (M0: 0) (M1: 1)	1.457	0.369	16.44	0.000
Type of operation (Transvesical · 0) (Transvesical 1)	−0.335	0.599	0.31	0.576
Histological differentiation (High or medium: 0) (Low: 1)	0.206	0 388	0.28	0.596
Transfusion (None. 0) (Transfusion · 1)	−0 325	0.334	0.95	0.329
Final model				
M stage (M0: 0) (M1: 1)	1.515	0.327	21.4	0.000

In the primary Cox regression model for prostate cancer specific survival (Table 3) the variables age, T stage, type of operation and transfusion were insignificant (in all cases $P>0.2$), while the M stage was highly significant ($P<0.000$). The effect of the M stage in the final model corresponds to an excess intensity of prostatic cancer deaths in patients with metastasis by a factor of 4.54 (95% confidence limits: 2.36–16.8).

In an intermediate model which included M stage, age and transfusion, the regression coefficient for transfusion was −0.4472 (SD=0.3112; $P=0.13$). This corresponds in the transfused group to a reduction in the prostatic cancer death rate to 0.64 (95% confidence limits: 0.34–1.19) of the death rate in the non-transfused patients.

Discussion

The results of the present study do not support the hypothesis that peri-operative blood transfusion promotes recurrence and death after surgery for prostatic carcinoma. The transfused patients had a slightly poorer survival than the non-transfused patients, but this was not statistically significant. When the effect of uneven distribution of risk factors was accounted for by Cox regression analysis, the overall effect of blood transfusion was a slight (not statistically significant) reduction in the prostatic cancer death rate.

The result of the present study is at variance with the conclusion in the report by Heal *et al.* (1988). These authors excluded patients with metastatic disease. We have reanalysed the present data after excluding patients with metastasis, but obtained essentially the same result.

The present study (like other studies in which no adverse effects due to blood transfusion could be demonstrated) may be criticised on a number of points. From a methodological point of view, the limited sample size and the retrospective acquisition of data, with resulting inaccuracy or bias, may have masked a real effect, leading to a statistical type-2 error.

A more specific criticism has been raised by Blumberg *et al.* (1986). They claimed that the detrimental effect of blood transfusion was due to a plasma factor. Consequently, transfusion of plasma-poor products could have masked a real effect in studies showing no demonstrable effect of transfusion. In the present study only 2 patients received plasma-poor products, and the negative result cannot therefore be ascribed to transfusion of plasma-poor products.

The fundamental problem in any discussion on the possible association between blood transfusion and the various adverse effects reported is whether the association is a causal one, or whether transfusion and the adverse effects merely have a common underlying cause. Cox regression analysis is a powerful tool in the evaluation of the relative influence of various well defined and accurately recorded background variables on survival parameters. However, it cannot deal with ill defined or unrecorded variables such as biologically aggressive tumours or difficult surgery, both of which we suspect to be possible common underlying causes.

A scientifically valid answer can be obtained only from randomised clinical studies, but the risk of transmitting blood-borne diseases makes such studies difficult to conduct. Instead, we recommend that blood transfusion be recorded as an additional variable in all future prospective studies on surgery for prostatic cancer, and that transfusion be included in the survival analysis.

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Effect of Catheter Material on the Incidence of Urethral Strictures

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Summary—The aetiology of urethral strictures in patients catheterised for short periods at the time of surgery is the subject of some debate. The occurrence of epidemics of strictures associated with certain batches of latex catheters, and the demonstrable *in vitro* cytotoxicity of latex in general, have supported the suggestion that catheter material (and in particular latex) has an important role.

We have looked retrospectively at 299 patients undergoing transurethral resection of the prostate gland by 1 urologist, 135 of whom had a latex catheter and 164 a plastic one; 19 patients developed strictures over the next 12 months with no proven difference attributable to the catheter material.

The study provides no evidence that the short-term use of latex catheters is associated with stricture formation.

The probability of a 40-year-old man requiring surgery for benign prostatic obstruction if he lives to 80 years of age has been estimated to be 10% (Lytton *et al.*, 1968), and operations on the prostate gland are the most frequently performed surgical procedures in men over 65 (Glynn *et al.*, 1985). Transurethral resection of the prostate (TURP) is safe (Chilton *et al.*, 1978) but approximately 6% of patients will develop new urethral strictures post-operatively (Lentz *et al.*, 1977), representing a significant morbidity.

The aetiology of these strictures has been the subject of considerable debate. Pre-operative factors are said to include the presence of an indwelling catheter (Jorgensen *et al.*, 1986) and infection or stricture (Lentz *et al.*, 1977) prior to resection. The most important operative factor appears to be urethral abrasion by the movement of the resectoscope during surgery (Emmett *et al.*, 1963) and several other authors (Bailey and Shearer, 1985; Schultz *et al.*, 1989) have suggested the use of a preliminary internal urethrotomy to minimise this. Other operative factors may include the experience of the operator (Lentz *et al.*, 1977), the lubricant used (Smith and Neligan, 1982; Walsh, 1982) and even the surgeon's glove talc (Fraser *et al.*, 1982).

Between 1979 and 1982 there was a surge of reports of troublesome urethral strictures in patients catheterised for short periods during cardiac (Sutherland *et al.*, 1983; Ruutu *et al.*, 1984) or prostatic surgery (Syme, 1982). Previous work (Keitzer *et al.*, 1968; Painter *et al.*, 1971; Edwards and Trott, 1973) had already shown a definite relationship between catheter material and the degree of urethral reaction, and further studies of the cytotoxicity *in vitro* of catheter materials confirmed this (Wilksch *et al.*, 1983; Ruutu *et al.*, 1985; Garred *et al.*, 1989). Clinically, the use of silicone or plastic catheters rather than latex ones significantly reduces the incidence of urethritis (Edwards *et al.*, 1983; Nacey *et al.*, 1985) but whether this results in a fall in the incidence of strictures has not been proven (Hart and Fowler, 1981; Goodwin and Chester, 1990).

To investigate the effect of catheter material on the symptomatic stricture rate in the 12 months following TURP we have retrospectively reviewed the records of patients receiving either latex or plastic catheters for post-operative drainage.

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Patients and Methods

The records of 301 consecutive patients who underwent TURP by 1 surgeon (J.T.F.) between January 1986 and May 1988 were reviewed at least 12 months after surgery. In January 1987 the type of catheter used for post-operative drainage was changed from latex to plastic; all other apparent factors remained the same.

Under either general or spinal anaesthesia the genitalia were cleaned with cetrimide 0.5% w/v and chlorhexidine 0.05% w/v (Pharmaceutical Service, Leicestershire Area Health Authority), and lignocaine hydrochloride 1% with chlorhexidine gluconate 0.25% gel (Biorex Laboratories Ltd, London) was instilled into the urethra. A preliminary cystoscopy was performed using a 15.5 F Storz 30° scope to record the degree of bladder trabeculation (none, mild, moderate or severe) and assess the diameter of the urethra. Pre-operative urethral dilatation was performed in 166 patients where the urethra was felt to be too narrow. The resections were performed with a Storz resectoscope via a 24 F sheath (except for 12 resections performed with a 27 F scope) using 1.5% glycine as the irrigant. The weight of gland resected was recorded to the nearest 5 g.

At the end of the resection 135 patients (mean age 71.3 years, SD ± 8.5) had a latex catheter inserted (Folatex haematuria 3-way Foley catheter, Eschmann Healthcare, Lancing) and 164 patients (mean age 72.3 ± 8.6 years) had a plastic catheter (Soft Simplastic 3-way haematuria Foley catheter, TFX Medical, High Wycombe). Two patients received an alternative type of catheter and were excluded from the comparison, although not from the overall figures. Sixteen patients had a 22 F latex catheter and 1 a 22 F plastic catheter; the other patients received 20 F catheters.

Continuous irrigation with 0.9% NaCl was used during the first 18 to 24 h post-operatively, using a closed drainage system. Pre-and post-operative antibiotics were used only if routine urine microscopy showed $> 10^5$ organisms/ml. The catheter was left *in situ* for 48 h or until any haematuria had cleared.

All patients were reviewed at 6 weeks and discharged if asymptomatic. The patients' records were examined at least 1 year after their TURP (84% of strictures having been shown to occur within 3 months) (Schultz *et al.*, 1989), with a range of 1 to 12 months (Jorgensen *et al.*, 1986). It was assumed that since this unit provides the only urology service in the Leicestershire area, all post-operative problems would present to us. Patients who died within 1 year of their TURP were excluded from the study.

All factors thought to contribute to stricture formation were recorded and the data entered on a main frame computer. The 299 patients were then separated into 2 groups according to the type of catheter inserted. Baseline differences in explanatory variables between the 2 groups were sought using the χ^2 tests (categorical variables) or Mann Whitney U tests (continuous variables); P values <0.05 were considered to be statistically significant. The patients who developed strictures were analysed to determine whether the catheter type or any other aetiological factor had been significant. Those factors found to be significant in the formation of strictures were then controlled for in a multivariate analysis of the effect of catheter material on stricture formation.

Results

The 2 groups of patients (135 with latex catheters and 164 with plastic) proved to be significantly different in several ways. Their mode of presentation was different ($\chi^2 = 11.228$ with 5 degrees of freedom (DF)) ($P < 0.05$), with more patients in the latex group being routine admissions for TURP compared with the Simplastic group, where a greater percentage presented in either acute on chronic retention (acute retention with a volume of retained urine > 1000 ml) or with symptoms of chronic retention with overflow (Fig. 1). This in turn meant that a greater proportion of patients with Simplastic catheters had a period of pre-

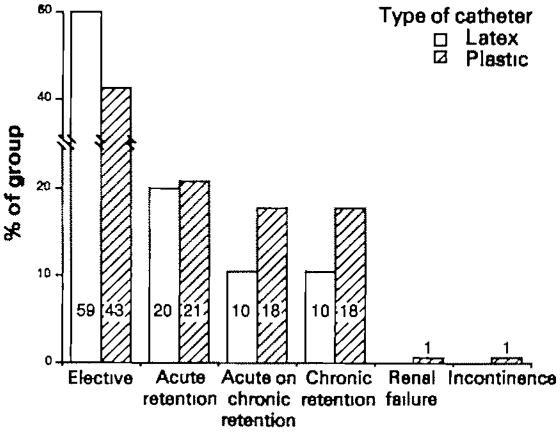

Fig. 1 Mode of presentation of the 2 groups.

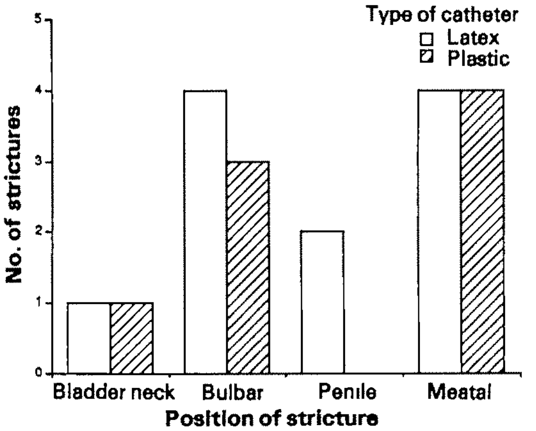

Fig. 2 Position of the 19 strictures noted at preliminary cystoscopy.

operative catheter drainage (χ^2 7.228, DF2) ($P<0.02$).

There was no significant difference ($P>0.1$) between the 2 groups in the number of strictures noted at preliminary cystoscopy (Fig. 2), with 11 of the 19 patients with pre-operative strictures receiving a latex catheter. There was, however, a difference in the number of patients who had previously had a TURP, with only 1 of 10 such patients being in the latex group.

The incidence of positive urine microscopy was recorded both pre-and post-operatively. Pre-operatively, 17.3% of patients (20% of the latex and 15.3% of the plastic groups) had a urinary tract infection (UTI). Post-operatively, this fell to 15.3% (14.1 and 16.5% respectively). Coliform bacilli accounted for 48% of these, with *Staph. albus* accounting for a further 21%.

At the time of surgery there was a significant change in the type of anaesthetic administered over the period of the study (Table 1). Overall, 55% of patients required urethral dilatation prior to resection (56% and 54%). The degree of bladder trabeculation noted at the initial cystoscopy was similar (χ^2 5.613, DF3) ($P>0.1$), as was the median weight of prostate resected (20 versus 25 g) ($P=0.08$), the distribution being skewed to the right (Fig. 3). Histological examination of the resected specimens showed 12% of both groups to contain at least foci of adenocarcinoma.

Table 1 Significant ($P<0.01$) Increase in Proportion of Patients having General Anaesthesia

	*Latex (%)**	*Plastic (%)**
Spinal anaesthesia	115 (85)	117 (71)
General anaesthesia	20 (15)	47 (29)
Total	135	164

*Column percentages.

In both groups, 96% of resections were performed using a 24 F resectoscope, but a 22 F latex catheter was used in 16 patients where haemostasis was felt to require it; only 1 patient required this size of plastic catheter. Although the majority of both groups had a 20 F catheter, there was a significant ($\chi^2=17.432$, DF1) ($P<0.001$) change in practice.

Post-operatively, 75% of patients required only 2 days of catheter drainage; any patient requiring a catheter for more than 7 days received a Silastic one. Table 2 shows the lack of difference between the 2 groups ($P>0.1$).

Table 2 Duration of Catheterisation following Surgery

Duration (days)	*Latex (%)**	*Plastic (%)**
2	107 (79)	116 (71)
2–7	17 (13)	31 (19)
7–42	4 (3)	10 (6)
>42	7 (5)	7 (4)

*Column percentages.

In the latex group, 7 patients (5.2%) developed a symptomatic stricture within the first year following TURP compared with 12 (7.3%) of those receiving plastic catheters (6.3% overall) (Fig. 4). There was no significant difference in the incidence of stricture formation related to the catheter material (χ^2 0.566, DF1) ($P>0.1$). The relative risk of stricture formation latex:plastic was 0.69 (95% confidence interval 0.25–1.84).

When the patients who developed strictures were compared with those who did not, several factors were found to be related to stricture formation. The occurrence of a post-operative UTI ($n=46$) was a significant predictive factor ($P<0.05$), with 6 patients (13%) developing strictures compared with 5% of uninfected patients. Three of the 10 patients who had previously undergone a TURP developed strictures ($P<0.01$), and 19% of patients whose resections contained adenocarcinoma went on to develop strictures compared with only 5% of benign resections ($P<0.001$). There was a significant trend (χ^2 5.191, DF1) ($P<0.025$) in the increase in stricture formation as the duration of post-operative

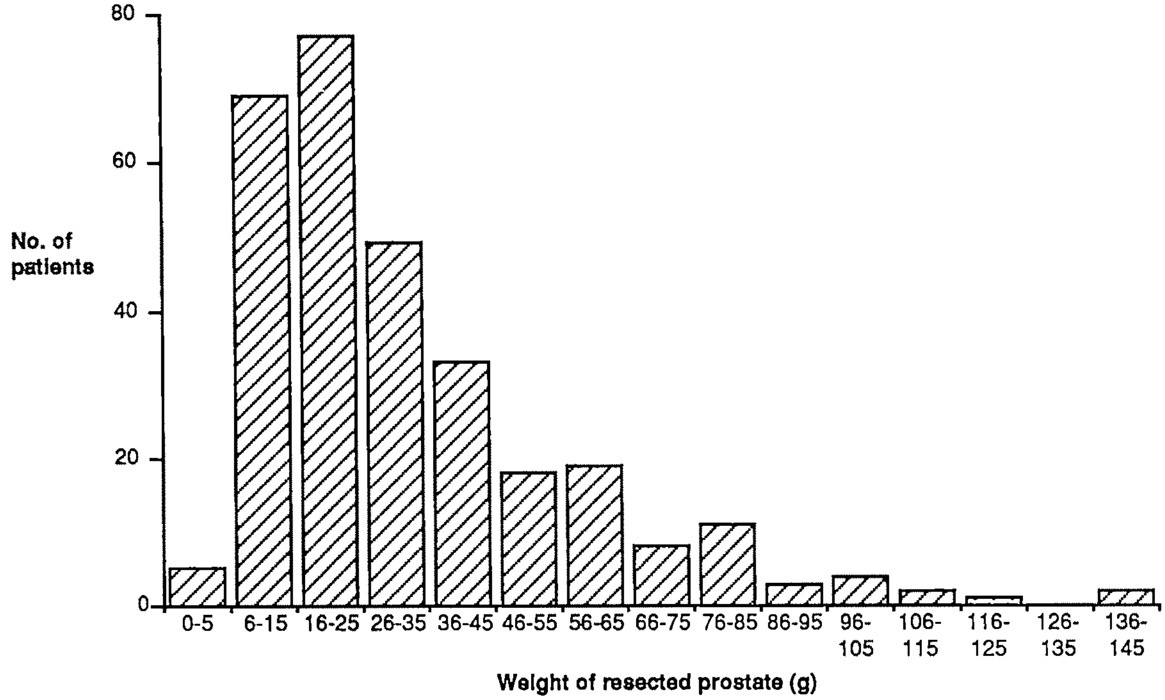

Fig. 3 Weight distribution of resected prostates for all patients

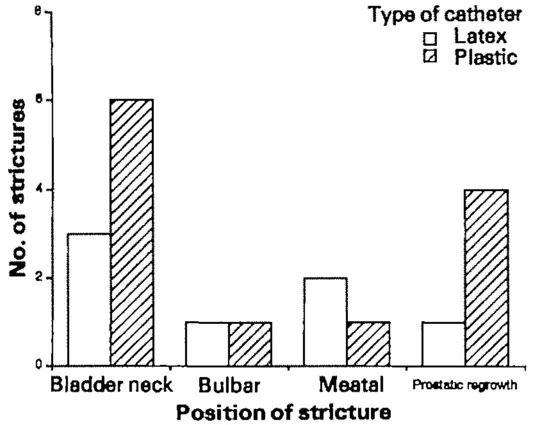

Fig. 4 Position of post-operative strictures

catheter drainage increased (Table 3), with the incidence of stricture formation rising from 4.9% in those who required only 2 days of catheter drainage to 21% in those who required a catheter for more than 42 days.

Three (15.8%) of the patients with pre-operative strictures developed further strictures (2/11 in the latex group and 1/8 in the plastic group) compared with 5.8% of those with normal pre-operative urethrae. The small numbers involved make this difficult to interpret.

A multiple logistic regression analysis model was constructed using stricture/no stricture as its binary response variable and post-operative UTIs, previous TURPs, histology, duration of catheter drainage post-operatively and patients with pre-

Table 3 Increase in Post-operative Stricture Rate with the Duration of Post-operative Catheterisation

Duration (days)	*Post-operative stricture (%)**	*No post-operative stricture (%)**
2	11 (5)	212 (95)
2–7	3 (6)	45 (94)
7–42	2 (14)	12 (86)
>42	3 (21)	11 (79)

*Row percentages.

vious strictures, together with catheter type as explanatory covariates. This model was shown to provide an adequate fit to the observed data. Having adjusted for the potential confounding factors, the relative risk of stricture formation was only marginally altered, being 0.74 latex:plastic (95% confidence limits 0.26–2.15).

Discussion

The decision to change from a 3-way haematuria catheter made of latex to a PVC/plastic one in January 1987 was made on the basis of several reported advantages in the use of the latter material. These include the large internal diameter, strong non-collapsible yet soft material, high irrigation flow rate, non-water-absorbent material decreasing catheter encrustation and biocompatibility, with the lack of cytotoxicity reducing stricture formation (Manufacturer's information on Simplastic urological catheters, 1989).

There appears to be no doubt that certain batches of latex catheters in the early 1980s were associated with epidemics of urethral strictures after short-term use (Ruutu *et al.*, 1982) and that this was related to their cytotoxicity (Ruutu *et al.*, 1985). *In vitro* studies since then have implied that latex catheters in general, because of their greater cytotoxicity, produce an increase in urethral stricturing. Clinical studies have appeared to support this suggestion (Ferrie *et al.*, 1986) but have been flawed by the use of controls catheterised with the same brand of latex catheter implicated by others in stricture epidemics (Sutherland *et al.*, 1983).

The suggestion that "where a catheter is considered essential it would seem sensible to use a silicone rather than a latex catheter" (Ferrie *et al.*, 1989) has major cost (and perhaps medico-legal) implications for the health service and there is little evidence to support it.

The present study was designed specifically to examine whether the short-term use (<7 days) of latex catheters was associated with an increase in urethral strictures when compared with the short-term use of plastic catheters. Despite some significant differences between the 2 groups, catheter material was found to have no discernible effect on stricture rate. If anything, the rate of stricture formation was lower among those with latex catheters (0.74:1 adjusted for potential confounding factors). It is important to recognise, however, that the confidence limits of this include possible beneficial and detrimental effects of latex which could be considered clinically relevant. Nevertheless, it may be estimated from our results that the probability of the true risk of stricture formation due to latex being more than 1.5 times greater than that due to plastic is less than 10% and it seems unlikely that a larger study would demonstrate an excess risk of any import.

While the other advantages of plastic catheters in terms of wide bore drainage continue to justify the slightly greater expense (£5.00:£7.69) in the case of patients undergoing TURP, our findings fail to support the suggestion that their use for routine short-term urine drainage increases the incidence of urethral stricture.

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Penile Strangulation

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Summary—Penile strangulation is a rare injury that requires urgent management. Non-metallic, thin objects are easy to remove but can cause severe injury. Metallic objects are difficult to remove but the injuries are usually less severe. Penile ulceration and oedema in children may well indicate the presence of a strangulation object. We describe a new hammer and chisel method for removing such objects.

Penile strangulating objects are usually rings, nuts, bushes and sprockets in adults, while in children they tend to be rubber bands, thread or hair. In adults the objects are placed deliberately by the person himself for masturbation or by his female partner to prolong erection (Browning and Reed, 1969). Strangulating objects in children are used to prevent enuresis and incontinence or as an innocent childish experiment. Various types of penile strangulation and their management are presented.

Patients and Methods

Eight patients have been treated since May 1985 and their strangulation injuries were graded as follows:

Grade 1	Oedema of distal penis. No evidence of skin ulceration or urethral injury.
Grade 2	Injury to skin and constriction of corpus spongiosum but no evidence of urethral injury. Distal penile oedema with decreased penile sensation.
Grade 3	Injury to skin and urethra but no urethral fistula. Loss of distal penile sensation.
Grade 4	Complete division of corpus spongiosum leading to urethral fistula and constriction of corpus cavernosum with loss of distal penile sensation.
Grade 5	Gangrene, necrosis or complete amputation of distal penis.

With one exception, all patients were of normal intelligence. Those aged between 5 and 16 years had injuries from non-metallic objects. In patients aged between 15 and 56 years metallic objects were involved. The periods of strangulation varied from 10 to 12 days. Metallic objects were 0.3 to 3 cm in thickness. One of the patients in this group put a ring over his penis (Figs 1 and 2). This led to severe oedema and retention of urine and he was forced to seek medical advice. All patients presented with distal penile oedema. Other complaints included ulceration, loss of sensation, decreased sensation, retention of urine and urethral fistula. Strangulation

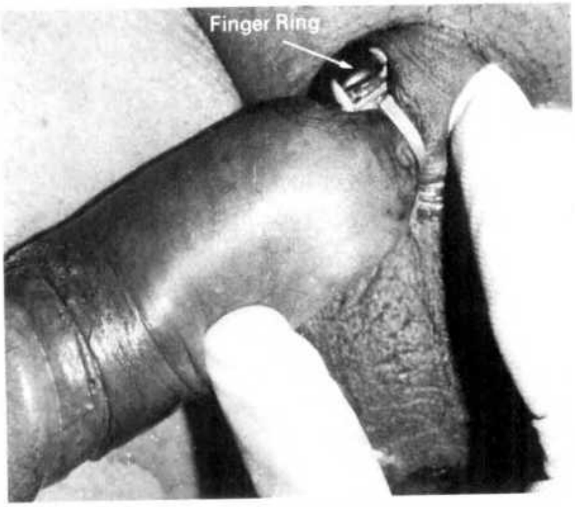

Fig. 1 Ring at root of penis with distal penile oedema.

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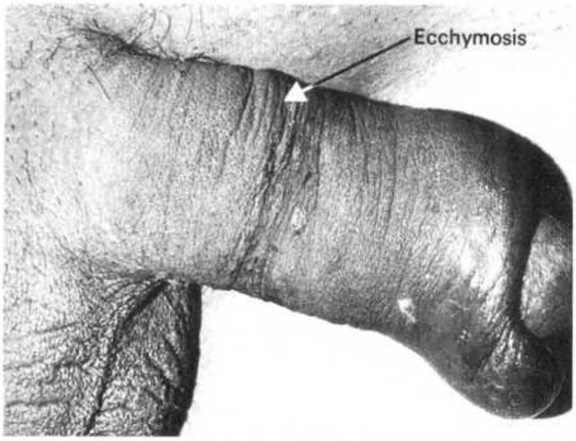

Fig. 2 Penis after removing ring. Arrow shows area of ecchymosis.

injuries were grade I in 1 patient, grade II in 2, grade III in 3 and grade IV in 2. There were no grade V injuries (Table 1).

In the non-metallic group of patients the injuries were severe (Grades III and IV) and the objects were removed with scissors (Tables 1 and 2). In patient no. 3 the rubber band could be seen only after removing the scab (Fig. 3). A reconstructive procedure with suprapubic urinary diversion was required in 2 patients (Table 2).

In the metallic group the injuries were less severe (Grades I–III) and the objects were removed with a metallic cutter, saw, heavy drill or hammer and chisel (Table 1). When using the heavy drill to cut a ball bearing nut, water was poured continuously at the side of the cut; about 20 litres of water were required and it took about 1.5 h to cut the object in 2 places. During this procedure the penile skin was protected by wrapping the penis in a sponge and holding the nut with 2 pliers.

A new method was used in 1 patient. The strangulating object was cut in 2 places with the help of a hammer and chisel by holding the object with pliers and placing an iron support on the opposite side of the cut to provide a counter-force. The cut was extended until a very thin rim of metal was left, to avoid injury to the penis. This thin rim was dismantled by using 2 pliers, one holding the cut piece and the other holding the remaining part of the object. The metallic ring was then removed.

Results

All patients recovered well over periods ranging from 1 day to 4 weeks. The recovery period was 2 to 4 weeks for patients in the non-metallic group and 1 to 3 weeks for those in the metallic group (Table 2). One of the patients with a urethroplasty had mild narrowing at the site of the anastomosis and required urethral calibration. Decreased penile sensation returned to normal in 2 to 3 days; this took 3 to 4 weeks in patients with complete loss of sensation and 8 weeks in the patient with a ball-bearing nut. Patients continue to have good erectile function and no urinary symptoms.

Discussion

Penile strangulation, if unrelieved, may lead to penile engorgement, ulceration, necrosis of the spongiosum and cavernous tissue, urinary extravasation, fistula and even gangrene. The corpus spongiosum and urethra are covered by a thin layer of fibrous tissue and are therefore more susceptible to injury than the corpus cavernosum, which is covered by tunica albuginia, a dense fibrous layer (Bashir and Barbay, 1980). In children the constricting band, thread or hair (Sheinfeld *et al.*, 1985) may be buried in an oedematous ulcer or scab; penile oedema therefore calls for a high index of suspicion of a constricting band. It is easy to remove non-metallic constricting objects but the injury is severe, as they are thin and sharp. They require suprapubic urinary diversion and management of complications (Table 2). If the constricting object is very small it causes severe oedema of the distal penis

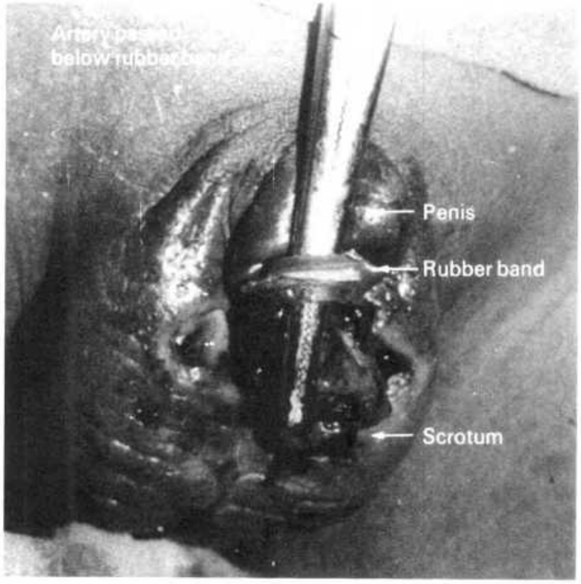

Fig. 3 Penoscrotal ulceration. Arrow shows constricting rubber band.

Table 1 Details of Patients

					Presenting complaints				
Case no.	*Age (years)*	*Mental function*	*Type of object*	*Duration*	*Distal penile sensation*	*Retention of urine*	*Penile oedema*	*Ulceration*	*Urethral fistula*
1	35	N	Finger ring	10 h	Decreased	Yes	Yes	No	No
2	25	N	Metallic nut (0.5 cm thick)	8 days	Absent	No	Yes	Yes	No
3	6	N	Rubber band	10 days	Absent	No	Yes	Yes	Yes
4	16	Retarded	Thread	6 days	Absent	No	Yes	Yes	Yes
5	5	N	Thread	12 days	Decreased	No	Yes	Yes	No
6	56	N	Ball bearing (3 cm thick	5 days	Absent	Yes	Yes	Yes	No
7	15	N	Metallic ring (0.3 cm thick)	4 days	Decreased	Yes	Yes	Yes	No
8	25	N	Metallic nut (0.5 cm thick)	5 days	Absent	Yes	Yes	Yes	No

Case no.	*Age (years)*	*Mental function*	*Grade of injury*	*Method of removal*	*Diversion*	*Additional surgery*	*Duration of recovery*	*Complications*
1	35	N	1	Metallic cutter	Nil	Nil	2 days	Nil
2	25	N	3	Hammer and chisel	UC	Nil	3 weeks	Nil
3	6	N	4	Scissors	SPC	Repair of urethral fistula	4 weeks	Nil
4	16	Retarded	4	Scissors	SPC	Repair of urethral fistula	4 weeks	Stricture
5	5	N	2	Scissors	Nil	Circumcision	5 days	Nil
6	56	N	3	Heavy drill	UC	Nil	2 weeks	Nil
7	15	N	2	Saw	UC	Nil	10 days	Nil
8	25	N	3	Saw	UC	Nil	2 weeks	Nil

N = Normal. SPC = Suprapubic cystostomy
UC = Via urethral catheter.

Table 2 Comparison of Metallic and Non-metallic Injuries

Type of object	*Age group (years)*	*Grade of injury*	*Urethral fistula*	*Duration of recovery (weeks)*	*Type of diversion*	*Reconstructive surgery*	*Complication*
Metallic	15–56	1–3	Nil	1–3	UC	Nil	Nil
Non-metallic	5–16	2–4	2 cases	2–4	SPC	2 cases	Stricture 1 case

UC = Urethral catheterisation.
SPC = Suprapubic cystostomy

and compression of the urethra, leading to acute retention of urine and early medical consultation, so that the prognosis is better in such cases (Table 1, Case 1).

The evaluation of penile strangulation includes assessment of temperature, colour, sensation, ability to void and pulsation distal to the strangulation; the latter is best evaluated by a Doppler flowmeter. Arteriography is probably of little value since the results may be questionable and time is wasted before the constricting band is removed (Snoy *et al.*, 1984). The technique of wood lamp examination after the intravenous administration of fluroscein has proved valuable in assessing blood flow to the skin distal to the constricting band (McGraw *et al.*, 1977). The choice of method for removing the object depends upon its type, size, how long it has been in place and the availability of equipment. Methods of removal include aspiration of corpora, ring removal, saws, grinders and dental drills

(Browning and Reed, 1969; Tiwari *et al.*, 1977; Snoy *et al.*, 1984).

Degloving of the penis may be used to remove nuts and the penis may be covered by partial thickness skin grafts. The removal of metal rings, nuts and bushes is difficult because of venous engorgement and the movement of saws and grinders may damage the penis. A dental drill or a carbide disc monitored by a dental drill is ideal in such circumstances. When a drill is used, water should be poured continuously to prevent heat injury, and caution is necessary to avoid avulsion of the penile skin. If a drill is not available, a hammer and chisel may be used to remove nuts. Although removal of metallic objects is difficult, the prognosis is good.

The urethra should be evaluated radiologically soon after removal of the constricting band. If grade 3, 4 or 5 injuries are found, suprapubic urinary diversion should be done. Simple emptying of the bladder by urethral catheterisation for 1 to 2 days may be required in grade 1 and 2 injuries. Devitalised tissue should be excised and skin replacement achieved with a graft or flap. Fenestrated skin grafts give good results as oozing of serum and blood occurs through them (Stoller *et al.*, 1987). Mild ulceration may heal following simple dressings but a urethral fistula may require a reconstructive procedure.

Post-operative recovery is directly proportional to the grade of injury. In grade 1 cases the distal penile oedema disappears immediately and penile sensation returns to normal within 4 h (case 1), but in grades 3 and 4 the return to normality may take 4 weeks (Table 2). The risk of complications increases with the higher grades of injury. Grade 5 injury is rare but its prognosis is poor.

Post-operative management should be directed towards preservation of skin and prevention of infection. Heparinisation should be considered if penile pulsation fails to appear within half an hour of removal of the constricting object (Snoy *et al.*, 1984). Urethral stricture (case 4) or priapism may be a late complication. During constriction there may be a partial nerve injury, but this usually heals within a week and penile sensation may return to normal. Should complete disruption of the nerve occur, it should be reapproximated and penile sensation will then return to normal (Best *et al.*, 1982). Previous reports of relatively good results from primary penile implants after amputation (Cohen *et al.*, 1977; Bux *et al.*, 1978) and good expertise in areas of urological and plastic microsurgical techniques may lead to the initial consideration of surgical amputation, band removal and reimplantation of the penis (Snoy *et al.*, 1984).

Penile strangulation is a serious injury but prompt attention and careful management can lead to full recovery with few complications.

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Management of Fracture of the Penis in Qatar

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Summary—We present 21 patients with fracture of the penis treated between July 1982 and July 1990. Eighteen patients were treated surgically, with good functional and morphological recovery; 3 refused surgery, 1 of whom had penile deformity and pain on erection. The literature is reviewed with respect to the necessity of different diagnostic and therapeutic options.

Fracture of the penis is a rare injury. The cause is usually direct trauma to the erect penis during violent sexual intercourse, forcible manipulation or turning over during sleep. Because the tunica albuginea is torn, it results in severe pain and immediate detumescence. Haemorrhage from the ruptured corpora cavernosa leads to swelling and deformity of the penis (Fig.). When Buck's fascia is torn, the haemoatoma extends to the scrotum, suprapubic region or the perineum. The corpus spongiosum and the urethra may be involved in severe injuries.

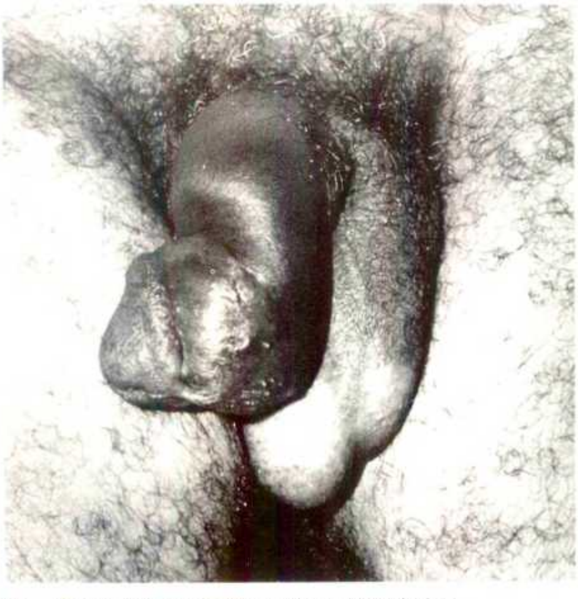

Fig. Fractured penis with swelling and deviation.

Published reports of this injury are so few that is difficult to draw firm conclusions as to the best treatment (Walton, 1979). Conservative management has been associated with complications, such as penile curvature, plaque formation causing Peyronie's-like disease or penile abscess formation, in approximately 29% of cases (Pryor *et al.*, 1981; Nicolaisen *et al.*, 1983). Therefore, there has been a definite trend in the literature towards immediate surgical management of this condition, which is reported to result in reduced complication rate and shorter hospital stay (Nicolaisen *et al.*, 1983; Naraynsingh and Raju, 1985; El Abd *et al.*, 1988). Although there is consensus that surgical treatment should consist of evacuation of the haematoma and repair of the tear in the tunica albuginea, there is still wide diversity in the pre-operative investigation and post-operative care of patients with this injury. We present our experience in the management of 21 patients with fracture of the penis, with a brief review of the world literature.

Patients and Methods

Between July 1982 and July 1990, 21 patients were admitted with the diagnosis of fracture of the penis. The aetiology of the fracture is shown in the Table.

Eighteen were treated by immediate exploration, evacuation of the haematoma and repair of the rupture of the tunica albuginea using absorbable

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Table Aetiology of Fracture of Penis

Aetiology	*No of cases*
Forcible manipulation	13
Direct blow to erect penis	3
Direct blow to flaccid penis	1
Sexual intercourse	2
Turning in bed	2
Total	21

sutures. The incision depended on the site of the fracture, being longitudinal or curved for basal and subcoronal circumferential, with degloving of the penis for distal fractures. Eleven fractures were at the base and seven were in the midshaft of the penis.

Three patients refused surgery and were treated conservatively. The first patient arrived at the hospital 4 h after injury. Iced compresses were applied to his genital area for a few hours. The second and third patients arrived 36 and 48 h later, respectively, and were merely observed for complications. The interval from injury to admission in the patients treated by immediate surgery ranged from 3 to 48 h (mean 9.8).

None of the patients was catheterised, nor were routine antibiotics or drugs administered to prevent early post-operative erection.

The average hospital stay was 4.1 days for the surgically treated group and 2.3 days for the group treated conservatively. Follow-up ranged from 3 to 66 months (average 11.5).

Nineteen patients were reviewed either during their regular follow-up appointments or after they had been called for the purpose of this study. Two patients treated surgically were lost to follow-up because they had left the country.

Results

The patients ranged in age from 22 to 58 years (mean 35). All except 2 were expatriates. Five patients were single (this group included the 2 non-expatriates), 3 were married and living with their wives, and 13 were married but unaccompanied by their wives.

Eighteen patients were treated by immediate surgery; 16 returned for follow-up. They had good erections with no post-operative or long-term complications such as penile deformity or plaque formation. One patient, of 2 who sustained the fracture during coitus, complained of mild pain with erection in the first 7 weeks. Two of the 3 patients treated conservatively had good erections; 1 of them had a transverse plaque measuring 1.0 × 0.4 cm in the penile shaft, at the site of the fracture. The third patient had weak erections accompanied by pain, deviation towards the right side, and palpable plaque at the base of the penis on the left side. The deformity did not interfere with his sexual performance. None of the patients sustained urethral injury.

Discussion

All patients treated by immediate surgery regained normal erections, while 1 of the 3 patients who refused surgery had weak and painful erections with obvious penile deformity. These results are similar to those reported in other series (Nicolaisen *et al.*, 1983, Fujisue *et al.*, 1984; Naraynsingh and Raju, 1985; Godec *et al.*, 1988).

Rupture of the corpus cavernosum is believed to occur only when the erect penis is subjected to a direct external force (Meares, 1971); nevertheless, such injury may be sustained while the penis is flaccid. One of our patients sustained a direct blow to his flaccid penis while playing football. Fujisue *et al.* (1984), in a review of 208 patients in the Japanese literature, found that 3% (6 cases) sustained the fracture while the penis was flaccid.

If we consider the relatively small population of the Arabian Gulf region, it would appear that fracture of the penis is commoner in this region than in other parts of the world. A total of 59 cases (including the 21 in this series) have already been documented in 3 hospitals whose catchment areas do not account for the whole population (Al Saleh *et al.*, 1985; El Abd *et al.*, 1988). Our results demonstrate that a large percentage of patients with this condition are expatriates who are single or married but not accompanied by their wives. They sustain the injury as result of forcible manipulation of an erect penis during masturabation or in an attempt to end prolonged erection. This distribution of social status was similar in other reports from the Gulf area (Al Saleh *et al.*, 1985; El Abd *et al.*, 1988). Only 2 patients in this series suffered the penile fracture during coitus, while in 13 it resulted from forcible manipulation. Comparable results were reported by Al Saleh *et al.* (1985) and El Abd *et al.* (1988). Similarly, Fujisue *et al.* (1984) found that 100 patients (48%) sustained the fracture by pushing and twisting or by masturbation; in only 37 cases (18%) did it occur during coitus. By contrast, Nicolaisen *et al.* (1983) found that 58% of their patients sustained the injury during sexual intercourse.

Fracture of the penis associated with urethral injuries usually occurred during sexual intercourse (Walton, 1979; Naraynsingh and Raju, 1985; Wespes *et al.*, 1987; Godec *et al.*, 1988). The frequency of urethral injuries ranged from 20 to 38% of cases reported from the USA and Europe (Walton, 1979; Parrillo *et al.*, 1981; Nicolaisen *et al.*, 1983; Naraynsingh and Raju, 1985; Wespes *et al.*, 1987; Godec *et al.*, 1988). By contrast, its frequency in the Gulf and Japan ranged from nil to 3% (Fujisue *et al.*, 1984; Al Saleh *et al.*, 1985; El Abd, 1988; Taha *et al.*, 1988). This difference could be explained by the fact that most of the injuries were caused by a relatively weak force during manipulation of an erect penis (Fujisue *et al.*, 1984).

There is clear diversity in the approach used to exclude urethral injuries in penile fracture. Some investigators perform a retrograde urethrogram in all such patients (Özen *et al.*, 1986; Taha *et al.*, 1988). We did not carry out this investigation and there were no untoward sequelae. Therefore we support the contention that this investigation should be performed only if rupture of the urethra is suspected from a history of voiding difficulty, bleeding from the external meatus, or gross or significant microscopic haematuria (Nicolaisen *et al.*, 1983; El Abd *et al.*, 1988; Orvis and McAninch, 1989).

Another area of dispute is whether or not a urethral catheter should be inserted. Several authors adopted its use in every case pre-operatively (Al Saleh *et al.*, 1985; Özen *et al.*, 1986; Taha *et al.*, 1988), per-operatively to exclude extension of the tear into the urethra (El Abd *et al.*, 1988) or post-operatively to serve as a urethral stent while a Koban pressure dressing is applied (Nicolaisen *et al.*, 1983). We believe that urethral catheterisation is unnecessary and should be avoided, particularly if urethral trauma is suspected. Inserting a urethral catheter in a fractured, deformed and swollen penis is painful to the patient and potentially harmful. The tip of the catheter may impale a contused area of urethral mucosa and convert this from a simple contusion into a tear through the full thickness of the urethral wall, or from a partial to a complete tear (McAninch, 1981; Mitchell, 1984). There is also the risk of introducing infection in an area of contusion or blood clot. Walton (1979) raised the question of whether much of the urethral damage seen at surgery in some of the reported series may have been produced by attempted urethral catheterisation.

Cavernosography has been advocated in order to diagnose and lateralise the rupture of the corpus cavernosum (Pliskow and Ohme, 1979; Dever *et al.*, 1983). In the present series, the diagnosis was based on the history and clinical findings, without the need for ancillary diagnostic tools. The 18 patients who were explored had a rupture in the tunica albuginea which was easily localised and repaired. The role of cavernosography should be limited in the management of fracture of the penis, particularly in view of the potential risks involved such as contrast reaction, increased fibrosis from extravasated contrast medium, and priaprism (Orvis and McAninch, 1989; Pliskow and Ohme, 1989). In doubtful cases, sonography may be used instead to confirm the diagnosis of penile fracture and to evaluate the integrity of the corpus spongiosum and urethra (Forman *et al.*, 1989).

We agree with those who believe it is not necessary to adminster antibiotics routinely (Nicolaisen, 1983; Orvis and McAninch, 1989). None of our patients treated surgically or conservatively received antibiotics and none showed any sign of infection.

Diazepam and stilboestrol have been used routinely to prevent erection in the early post-operative period (El Abd *et al.*, 1988; Taha *et al.*, 1988). We did not adminster such drugs and although some of out patients experienced erection in the first few post-operative days, no related complications ensued such as re-bleeding at the fracture site. In our experience, such erection is limited by the pain involved. Also, early erection does not exert undue tension on the skin suture lines, since the penile skin is lax after being stretched by the haematoma. Indeed we found that erection improved the patient's morale, for his anxiety lessened when he experienced erection post-operatively.

The hospital stay of the patients treated surgically was similar to that reported by Özen *et al.* (1986) and El Abd *et al.* (1988). However, this is the first study to document a shorter hospital stay in patients treated conservatively. The reason is that they had no medication nor any kind of catheterisation that would necessitate prolonged hospitalisation.

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Traumatic Rupture of the Corpus Cavernosum

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Summary—Twelve patients with fracture of the penis have been treated in this department during the last 18 years. Their mean age was 41.5 years (range 25–55) and two-thirds of the injuries resulted from coitus. Eleven patients underwent immediate exploration and repair of the tunica albuginea and only 1 still has sexual dysfunction. One patient was treated conservatively and remains impotent. Immediate surgical treatment is recommended, since it avoids the formation of penile plaque, penile fibrosis and angulation and accelerates restoration of normal penile function.

Penile fracture has been defined as rupture of the corpus cavernosum and/or spongiosum due to blunt or penetrating injury while the penis is erect. Injuries to the flaccid penis, or rupture of the suspensory ligament, are not included in this definition (Das and Amar, 1986). It is a rare condition, with little more than 100 cases having been previously reported (Meares, 1971; Godec *et al.*, 1988). The aetiology, clinical symptoms and pathological findings have been well described, but its treatment remains uncertain. The majority of authors reporting small numbers of patients recommend early surgical repair (Nicolaisen *et al.*, 1983; Klein *et al.*, 1985). This report describes the management and outcome in 12 patients with penile fracture seen in this institution over the last 18 years.

Patients and Methods

Between 1970 and 1988, 12 patients presented with penile fracture. Their ages ranged from 25 to 55 years (mean 41.5). In 8 patients the injury occurred during sexual intercourse, in 1 as the result of an assault during intercourse, in 1 during masturbation, in 1 from urination while the penis was erect and in 1 from an accidental blow with a piece of bamboo. The most frequent clinical findings were pain, swelling, angulation and local skin discolouration of the penis (Figs 1 and 2). A cracking sound occurred in only 7 patients. The interval between penile fracture and treatment ranged from 1 to 72 h. Emergency exploration was performed in 11 patients, using either a longitudinal or transverse incision over the site of maximum swelling. Only 1 patient had a coexisting injury to the corpus spongiosum. The rupture ranged from 0.7 to 3.5 cm and in 3 patients the size was not specified. Repair

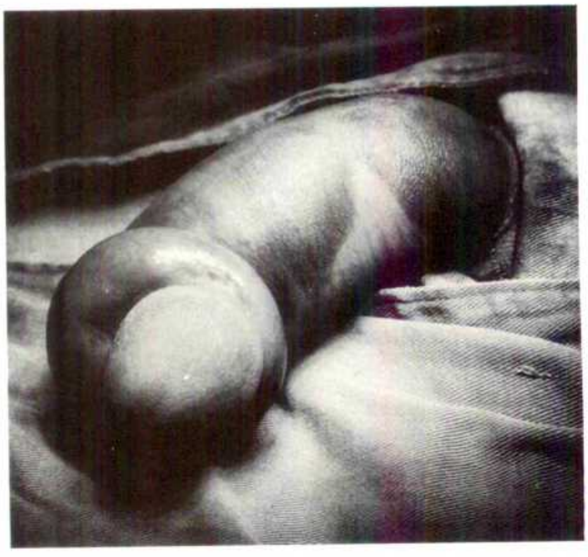

Fig. 1 Patient 7. One hour after injury, severe penile oedema, deformity and discolouration can be seen.

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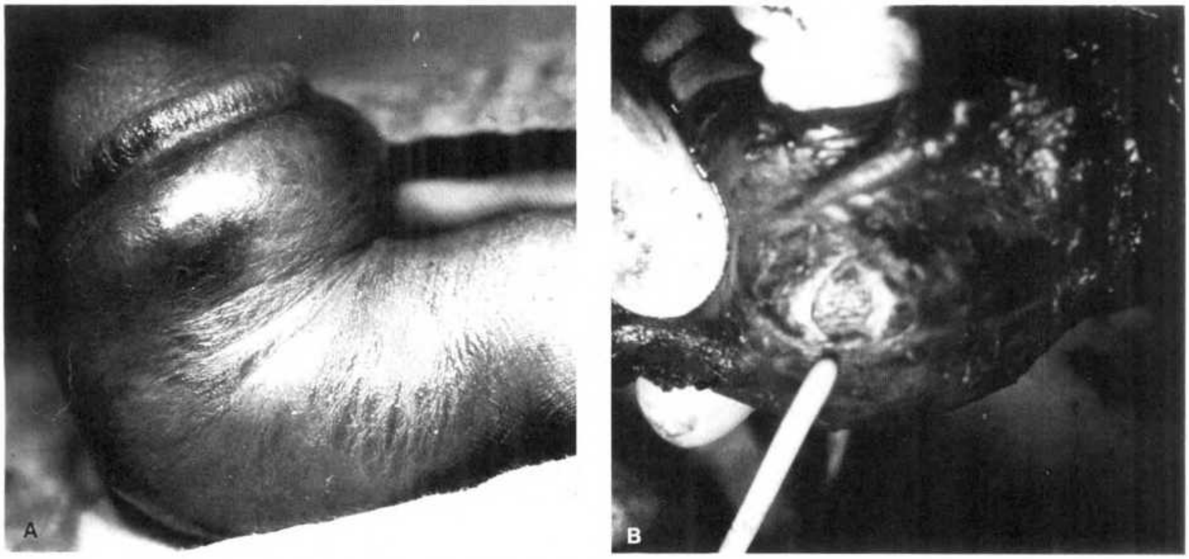

Fig. 2 Patient 8. (A) Twelve hours after injury, the ventral portion of the penis shows marked oedema and discolouration, together with deformity of the distal segment. (B) A circular incision was made on the penile skin of the coronal sulcus and the skin directed towards the proximal segment. A tear can be seen on the tunica albuginea.

of the tunica albuginea was performed with interrupted catgut or Dexon sutures. The laceration of the corpus spongiosum was considered too small to warrant repair. All patients were treated with an indwelling catheter and received prophylactic antibiotics; 8 received concomitant oestrogen therapy in order to prevent an erection. One patient was treated conservatively with incision of the penile skin and drainage of the haematoma, with no attempt made to treat or identify the ruptured corpus.

Results

The mean hospital stay was 8.4 days (range 2–14). One of the 8 patients who received oestrogens and 1 of the 4 patients who did not receive oestrogens had a painful erection. Long-term follow-up was by means of questionnaire. Two patients were impotent and this included the 1 who had undergone only incision and drainage of the haematoma and the patient who had sustained injury to both corpus cavernosum and corpus spongiosum.

Discussion

Fracture of the penis is rare, with little more than 100 cases being reported (Taha *et al.*, 1988). The majority occur during sexual intercourse and the incidence of 8/12 (67%) in this series corresponds with that of 58% reported by Nicolaisen *et al.* (1983). In the present study the mean age (41.5 years) was higher than the 26 years reported by Nicolaisen *et al.* (1983). The reason for this difference is not clear. Only 1 of our patients received a concomitant injury to the corpus spongiosum but it has been reported that approximately 25% of patients can be expected to incur injuries to both the corpus cavernosum and spongiosum (Nicolaisen *et al.*, 1983).

Many different conservative treatments have been used in this condition, including compression bandages, ice packs and anti-inflammatory agents (Farah *et al.*, 1978), streptokinase and streptodornase (Meares, 1971) and diethylstilboestrol or sedatives to suppress penile erection (Creecy and Beazlie, 1957; Jallu *et al.*, 1980). However, the results of such treatments were associated with penile deformity in 10% of patients, with suboptimal erections, difficulty with coitus and prolonged hospitalisation. Meares (1971), Nicolaisen *et al.* (1983) and Pryor *et al.* (1981) also used conservative methods to treat penile fractures. All of their patients developed a fibrotic lump, as well as angulation of the penis, which required a second operation. In this study the only patient who received conservative treatment also developed a fibrotic plaque and was unable to achieve a full erection.

The use of synthetic oestrogens to prevent painful erections is, in our experience, unnecessary. The excellent results achieved in 10 of 11 patients who underwent immediate surgical evacuation of the haematoma and repair of the ruptured tunica albuginia suggest that this is the treatment of choice, since it allows the penis to regain normal anatomical shape and physiological function and minimises the occurrence of sexual dysfunction.

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Erectile Response to Visual Erotic Stimuli Before and After Intracavernosal Papaverine, and its Relationship to Nocturnal Penile Tumescence and Psychometric Assessment

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Summary—Three methods of assessing erectile capacity—nocturnal penile tumescence (NPT), response to visual erotic stimuli (VES) and to intracavernosal papaverine (ICI)—have been assessed in 42 men presenting with erectile dysfunction. There was some overlap but also important differences between the 3 measures.

Subjects were divided into "high" and "low" NPT groups. The "high" group produced greater erectile responses to both VES and ICI. The combination of VES and ICI was the best discriminator of the two NPT groups, and may be of diagnostic value, particularly in younger men, reducing the need for repeated injections and higher doses of papaverine.

In the "low" NPT group, presumed predominantly organic, the ICI response correlated better than the VES response with NPT. In the "high" NPT group, the opposite applied, suggesting that in "psychogenic" cases, response to ICI may be modified by psychological mechanisms which could be of aetiological importance and which deserve further study.

These three methods should be regarded as measuring different aspects of erectile function and not as alternative diagnostic procedures. More research is required before their respective diagnostic values are established.

The current methods of investigating erectile dysfunction have 2 broad aims: first, the assessment of the man's capacity for erectile response, usually to distinguish between predominantly physical and psychological impairment; second, to identify specific pathological factors such as vascular or neurological disease, which may be contributing to the impairment.

Assessment of erectile capacity is of 3 kinds; measurement of spontaneous erections during sleep (Nocturnal Penile Tumescence, NPT), the erectile response to erotic stimuli measured in the laboratory, and the response to intracavernosal smooth muscle relaxants such as papaverine. The first 2 methods assess physiological responses, though their relevance to normal sexual function is not well understood; the third measures a pharmacologically induced response.

The relative diagnostic merits of these 3 methods are still debated and each has its shortcomings. NPT is expensive to assess, responses are often "borderline", neither clearly normal nor abnormal, and impairment can occur with a variety of conditions including peripheral vascular disease, neurological disease, endocrine disorder and depression. Its main advantage is that it is relatively free from psychologically mediated effects. Response to erotic stimuli, whilst possibly closest to normal sexual response, is susceptible to psychological factors, and may be normal in states of endocrine abnormality (Bancroft, 1988). Intracav-

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ernosal injection of smooth-muscle-relaxing drugs is a powerful way of inducing erection, to the extent that there is an appreciable risk of prolonged erection requiring pharmacological reversal. For this reason, it is usually necessary to start with a low dose, and consequently more than 1 injection may be required to establish the full response. Furthermore, whereas response to such drugs is likely to be impaired in cases of vascular aetiology, it may be normal or even enhanced in neurological cases. It is also now fairly clear that the erectile response can be inhibited by psychologically mediated mechanisms. In each of the 3 methods one can only draw firm conclusions from a normal or full response (Buvat *et al.*, 1990), which seriously limits their clinical usefulness. The diagnostic value of such methods will remain limited until we have a better understanding of the factors that influence each type of response.

The study reported here has 3 main aims: (i) to assess the combination of visual erotic stimuli and intracavernosal papaverine as a possible alternative to using either alone; (ii) to examine the relationship between these 3 methods of assessment, by comparing them in the same individuals, and to explore the extent to which they reflect different processes or different psychometric characteristics; and (iii) to assess the relative diagnostic values of the three methods in distinguishing between groups categorised on the basis of routine clinical assessment (*i.e.* sexual and medical history and routine physical examination).

Patients and Methods

Forty-two men, attending the sexual dysfunction clinic, received the 3 types of assessment as part of diagnostic screening to select subjects for a treatment study of a new dopamine agonist drug. The average age was 49.3 years (s.d. 11.7; range 24–73).

Measurement of erectile response to visual erotic stimuli and to intracavernosal papaverine

Erectile response was measured by means of a mercury-in-rubber strain gauge connected, through a Wheatstone Bridge, to a Grass 7PIE DC preamplifier in a Grass model 7D polygraph. The system was calibrated using two metal discs of diameters 25 and 26 mm to give a ratio of 2.5 mm of pen deflection to 1 mm of penile diameter change (Bancroft and Bell, 1985).

After fitting the strain gauge, the subject sat in a comfortable chair in front of a video monitor, and was asked to watch a series of 5 min video recordings, alternating between neutral (nature film) and erotic (showing normal heterosexual activity). After 2 neutral and 2 erotic films, the subject was given an intracavernosal injection of 30 mg of papaverine HCl. Five minutes after the injection a further series of 2 neutral and 2 erotic films were shown and the erectile responses measured.

Erectile response was analysed by measuring penile diameter at 1 min intervals during each stimulus and taking the mean level for each stimulus period.

In 16 subjects Doppler wave form analysis was carried out before and after the papaverine injection, together with measurement of pulse amplitude from the dorsum of the penis during response to the erotic stimuli and following papaverine, using a photometer according to the method described by Bancroft and Bell (1985). These results are of possible relevance to questions of aetiology, in particular to vascular impairment, rather than erectile capacity *per se*, and therefore will be reported separately.

Measurement of nocturnal penile tumescence

Nocturnal penile tumescence was recorded on 2 consecutive nights using the recording system described above. The following parameters were measured: (a) maximum increase in penile *diameter* (mm), (b) number of erectile episodes reaching a diameter increase of 15 mm or more, (c) number of erectile episodes reaching a diameter increase of 10 mm or more, (d) number of erectile episodes reaching a diameter increase of 5 mm or more, (e) time spent at tumescence above the 15 mm diameter increase, in seconds, (f) time spent at tumescence above the 10 mm diameter increase, (g) time spent at tumescence above 5 mm.

Psychometric assessment

Whilst attending for measurement of NPT, 38 subjects completed the following:

(a) *The Sexual Experience Scales (SES)* (Frenken and Vennix, 1980). This provides 4 scales as follows: (i) SES1, *the sexual morality scale*, refers to attitudes, norms and values concerning marital sexual behaviour, premarital sex and the sexual socialisation of children and young people. A high score reflects restrictive sexual morality, a low score permissive sexual morality. (ii) SES2, *the psychosexual stimulation scale*, refers to the extent that someone seeks or allows (rather than avoids or rejects) sexual stimuli of an auditory-visual or imaginary kind. The items refer to behaviour and experience in *non-interactional social-sexual situations*. A low score means high allowance of sexual stimuli or higher psychosexual arousability; a high score means non-involvement, avoidance, or rejection. (iii) SES3, *the sexual motivation scale*, refers to sexual interaction with one's partner: (a) degree of sexual response including actual and preferred frequency of sexual intercourse, (b) the extent of exploration of sexual sensations, (c) the occurrence and frequency of certain emotional reactions during foreplay, coitus and orgasm. A low score means a strong approach tendency or "sexual appetite"; a high score a strong avoidance tendency or "sexual aversion". (iv) SES4, *the attraction to marriage scale*, refers to 3 reasons a person may have for continuing or ending their marriage: (1) the social and emotional attraction to the partner, (2) the social and moral unacceptability of ending the relationship and (3) the sexual attraction of the partner. In contrast to the first 3 scales, *a high score means strong attraction to marriage.*

(b) *Golombok–Rust Inventory of Sexual Satisfaction (GRISS)* (Golombok and Rust, 1985). The male version of this short 28-item questionnaire gives an overall score and subscales for "impotence", premature ejaculation, male non-sensuality, male avoidance, male dissatisfaction, infrequency and non-communication.

(c) *Locke–Wallace Marital Adjustment Scale* (Locke and Wallace, 1959). This short 15-item questionnaire includes ratings of degree of agreement/disagreement in various aspects of marital life plus some more general questions about degree of happiness, shared interests and regrets about being married. Scores range from 2 to 158, and a score of 100 is regarded as a good discriminator between well adjusted (high score) and poorly adjusted (low score) marriages.

Clinical categorisation

Patients were categorised on the basis of their clinical history and physical examination into "Probable psychogenic" (n = 12, mean age 38.2 (± 8.2; 24–46)); "Probable vascular" (n = 11, mean age 58.1 (±8.2, 48–73)); "Other organic" (n = 8, mean age 53.6 (±10.7, 37–66)) and "Uncertain" (n = 12, mean age 50.4 (±9.6, 38–69)). The "uncertain" category was used for those who had neither clear evidence of psychogenesis, nor physical disease sufficient to be an obvious explanation. The "Other organic" group included 3 with neurological disease or damage, 1 of whom also had clear psychogenic factors. There were 3 Type II diabetics, 1 of whom showed clear psychogenic factors, and 2 of whom were in the vascular group; and one Type I diabetic who also had undergone renal transplantation. The "Psychogenic" group was significantly younger than the other three groups (*v.* "Uncertain", $P = 0.002$; *v.* "Vascular", $P < 0.001$; *v.* "Other organic", $P = 0.027$).

Results

In order to examine the relationship between our main variables, subjects are divided, according to the best median split, into 2 groups, *i.e.* "high" and "low" NPT, on the basis of their maximum NPT response. These 2 groups are then compared for the other variables.

Nocturnal penile tumescence (NPT)

The NPT parameters for Nights 1 and 2 are given in Table 1. The subjects were divided according to the maximum increase in penile diameter from the 2 nights of testing. The distribution of scores was bimodal with the median split at 9.5 mm increase in diameter (*i.e.* 32 mm increase in circumference). All subjects with a maximum less than 9.5 were in the "low" NPT group.

A "first night effect" was not apparent in the maximum responses, but was clearly present in the number of events greater than 5 mm increase in diameter, and, in particular, the time above 5 mm increase in diameter.

The NPT parameters for the "high" and "low" groups are shown in Table 2, showing a clear difference between them in most of the parameters analysed, except for those degrees or duration of

Table 1 First and Second Night NPT Results for Whole Group

	Night 1 (n=41) Mean (s.d.)	*Night 2 (n=42) Mean (s.d.)*	*P*
Max. increase diameter (mm)	7.5 (5.4)	7.8 (5.1)	n.s.
No. ev. > 15 mm (> 50 mm circumf.)	0.3 (1.0)	0.4 (1.6)	n.s.
Time > 15 mm (min)	2.6 (10.3)	2.2 (9.5)	n.s.
No. ev. > 10 mm (> 33.3 mm circumf.)	0.7 (1.4)	1.2 (2.1)	0.08
Time > 10 mm (min)	9.8 (23.1)	13.3 (25.5)	n.s.
No. ev. > 5 mm (> 16.7 mm circumf.)	1.7 (1.8)	2.3 (2.3)	<0.05
Time > 5 mm (min)	25.6 (35.1)	39.1 (49.7)	<0.01

n.s. $P > 0.1$

Table 2 NPT Data for Low and High NPT Groups

Night 1	*Low NPT (n=21) Mean (s.d.)*	*High NPT (n=20) Mean (s.d.)*	*P*
Max. increase diameter (mm)	3.8 (2.2)	11.4 (4.8)	*
No. ev. >15 mm (>50 mm circumf.)	0.0 (0.0)	0.6 (1.3)	0.06
Time >15 (min)	0.0 (0.0)	5.4 (14.4)	0.11
No. ev. >10 mm (>33.3 mm circumf.)	0.0 (0.0)	1.5 (1.8)	n.s.
Time >10 (min)	0.0 (0.0)	20.0 (30.2)	0.01
No. ev. >5 mm (>16.7 mm circumf.)	0.5 (0.7)	2.9 (1.7)	<0.0001
Time >5 (min)	4.0 (7.9)	48.3 (38.4)	0.0001
Night 2	*Low NPT (n=21) Mean (s.d.)*	*High NPT (n=21) Mean (s.d.)*	*P*
Max. increase diameter (mm)	3.7 (2.7)	11.8 (3.3)	*
No. ev. >15 mm (>50 mm circumf.)	0.0 (0.0)	0.8 (2.2)	n.s
Time >15 (min)	0.0 (0.0)	4.4 (13.3)	n.s
No. ev. >10 mm (>33.3 mm circumf.)	0.0 (0.0)	2.5 (2.3)	0.0001
Time >10 (min)	0.0 (0.0)	26.7 (31.0)	0.0008
No. ev. >5 mm (>16.7 mm circumf.)	0.6 (1.4)	3.9 (1.8)	<0.0001
Time >5 (min)	11.3 (29.2)	66.9 (51.0)	0.0001

* The variable on which median split is based
n.s. $P>0.1$

response which occurred infrequently in both groups. Had other parameters been used to categorise subjects, the composition of groups would have changed little. Thus, if number of "events" greater than 5 mm increase in diameter, or "time above 5 mm" had been used, 38 and 36 of the 42 subjects, respectively, would have remained in the same groups.

Response to visual erotic stimuli (VES) before and after intracavernosal papaverine (ICI)

Mean increases in penile diameter during neutral and erotic stimuli before and after papaverine, for the "high" and "low" NPT groups are shown in Table 3 and Figure 1. Data from these 2 groups were subjected to a 2 × 2 × 2 × 2 ANOVA of erectile responses during the test situation, involving, as additional factors, "injection" (*i.e.* response before and after papaverine), "stimulus" (*i.e.* erotic *v.* neutral) and "order" (*i.e.* first or second film).

In both high and low NPT groups, the response to erotic stimuli is greater to the first than to the second erotic film, before and after the injection (F=26.84, df=1,36, $P<0.0001$). The "high" NPT group showed greater levels of response throughout the test (F=10.45, df=1,36, $P=0.0026$). The effects of the papaverine injection and the exposure to erotic films were both highly significant (respectively, F=94.87, df=1,36, $P<0.0001$; F=53.86, df=1,36, $P<0.0001$). A significant interaction was found between Group (High and Low NPT) and Injection (*i.e.* before and after papaverine) (F=5.97, df=1,36, $P=0.02$) and between Group and Content of stimulus (F=7.21, df=1,36, $P=0.011$). Thus we can conclude that the High NPT group showed greater response to the erotic films and a greater response to the papaverine.

In Table 3, the *P*-values are derived from *t*-tests between groups. These show that, following papaverine, although the high NPT group had signifi-

Table 3 Mean Penile Diameter (mm) during "VES and Papaverine Test" in Low and High NPT Groups

	Low NPT		*High NPT*		
Phase	*n*	*Mean (s.d.)*	*n*	*Mean (s.d.)*	*P*
Before injection					
Neutral	21	0.01 (0.13)	21	0.07 (0.58)	n.s
Erotic	21	2.02 (1.98)	21	4.05 (3.56)	0.03
Neutral	20	0.46 (0.57)	21	1.15 (2.89)	n.s.
Erotic	19	1.37 (1.45)	20	2.63 (2.59)	0.07
After injection					
Neutral	21	3.01 (1.7)	21	5.16 (3.51)	0.02
Erotic	21	4.75 (2.92)	21	8.2 (3.85)	0.002
Neutral	21	3.61 (3.08)	21	6.05 (4.06)	0.04
Erotic	20	3.98 (2.84)	20	7.19 (3.84)	0.005

N.B. Scores given are means for the 5 readings, sampled at minute intervals, for each neutral and erotic stimulus

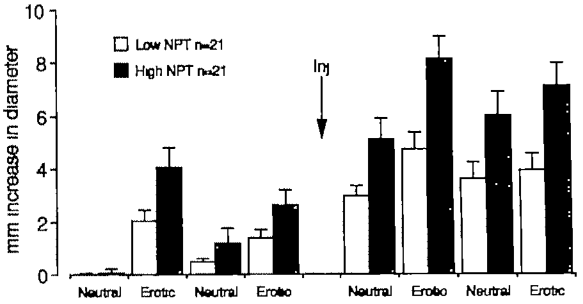

Fig. 1 Increase in penile diameter in the "High" and "Low" NPT groups of men in response to sequences of 5 min neutral and erotic films before and after 30 mg of intracavernosal papaverine (Inj.). Values given are means (and s.e.s) of 1 min samples of penile diameter

cantly greater penile diameter during both the neutral stimuli, the difference between groups was substantially greater when responses to the erotic stimuli were compared. Thus, the use of visual erotic stimuli enhanced the discrimination of these 2 groups by the papaverine injection.

The possibility that papaverine may have enhanced the erectile response to erotic stimuli was also examined. This was found not to be the case in general. The additional effect of exposure to the erotic stimulus (*i.e.* mean response during the erotic stimulus minus mean response during the neutral stimulus immediately preceding it) is shown in Table 4. This indicates that in both groups this "additional effect" is less after the injection than before. This presumably reflects the limited capacity for response, which is closer to the ceiling after the injection than before, the ceiling being lower in the "low" NPT group. It is interesting to note, however, that 4 men went against the general pattern, showing greater erectile response to the erotic films after the injection than before, suggesting that in some way the papaverine enhanced the response to these psychically mediated stimuli. The responses of these 4 men are shown in Figure 2, together with details of their NPT response and clinical diagnosis.

The maximum NPT response was significantly greater than the maximum response to erotic stimuli *before* the injection in both the "High" and "Low" NPT groups (for the "High" group, -max NPT 13.8 (s.d. 3.2); max erotic 6.2 (s.d. 4.6); $t=7.48$; $P<0.001$; for the "Low", max NPT 4.71 (s.d. 2.4); max erotic 3.15 (s.d. 2.7); $t=2.01$, $P=0.058$). *After injection* the maximum response was still less than the maximum NPT response in the "High" NPT group (max NPT 13.8 (s.d. 3.2); post-injection max 10.26 (s.d. 4.6); $t=3.01$, $P=0.007$). By contrast, in the "Low" NPT group, the max NPT was slightly but not significantly less than the post-injection maximum (4.71 (s.d. 2.4) and 5.86 (s.d. 3.9) n.s.).

Product-moment correlations between variables,

Table 4 Increase in Penile Diameter (mm) during Erotic Films for Low and High NPT Groups before and after Papaverine Injection (Differential Values: Erotic Minus Preceding Neutral)

	Low NPT		*High NPT*		
Phase	*n*	*Mean (s d.)*	*n*	*Mean (s d.)*	*P*
Before injection					
Erotic 1	21	2.01 (1.92)	21	3.98 (3.75)	0 04
Erotic 2	19	0.96 (1.19)	20	2 05 (2 4)	0.08
After injection					
Erotic 1	21	1.74 (2.05)	21	3.05 (2.42)	n.s
Erotic 2	20	0.87 (1.28)	20	1.41 (2 15)	n.s.

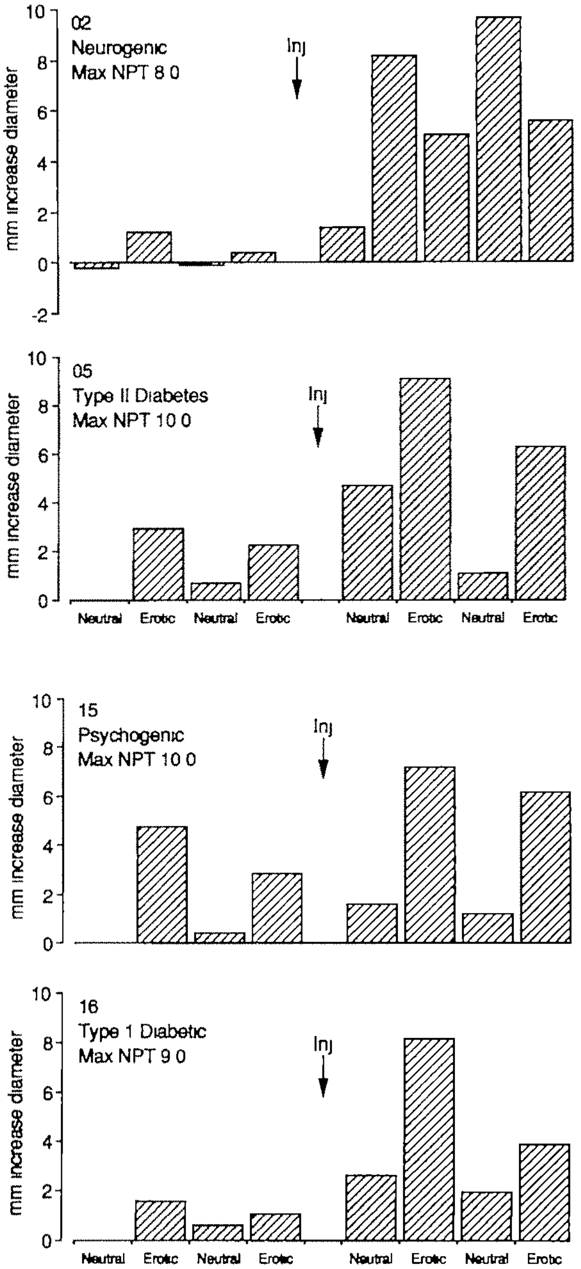

Fig. 2 Erectile responses to sequences of 5 min neutral and erotic films before and after 30 mg of intracavernosal papaverine (Inj.) in 4 individual subjects who showed an enhanced response to the erotic stimuli after the papaverine. The study number, diagnostic category and maximum NPT response is shown for each individual

and a step-wise multiple regression using NPT response as the dependent variable and response to erotic stimuli and to papaverine as the independent variables, were also carried out. The correlations between the various NPT parameters and the responses to erotic stimuli, before and after papaverine, and the response to the papaverine alone (*i.e.* during first neutral stimulus after injection) are shown in Table 5. In most respects, and taking the group as a whole, the NPT parameters correlate better with the responses involving erotic stimuli. The best correlation with response to the papaverine *per se* involves NPT time over 5 mm increase in diameter. In the step-wise multiple regression, in which maximum NPT response was the dependent variable, maximum response to erotic stimuli was entered first (r = 0.44). The inclusion of response to the papaverine (*i.e.* during the first neutral stimulus following injection) added little (multiple r = 0.47, explaining 23% of the variance).

Table 5 Correlation between NPT and Response to Erotic Stimuli and Papaverine Injection

	Max response to VES	*Response§ to ICI*	*Max. response to VES after ICI*
Max. inc. over 2 nights	0.44**	0.36*	0.49**
No. ev. >5†	0.37*	0.33*	0.36*
No. ev. >10†	0.34*	0.26	0.29
Time >5†	0.47**	0.49**	0.36*
Time >10†	0.48**	0.29	0.28

† average of two nights * $P<0.05$ ** $P<0.01$
§ Response during first neutral stimulus after, minus first neutral before, injection

However, when correlations are examined within the "High" and "Low" NPT groups separately, some interesting differences emerge. Thus in the "High" group, maximum NPT response correlates weakly with maximum response to erotic stimuli before papaverine (r = 0.34; $P = 0.12$), but correlates even less with maximum response to erotic stimuli after papaverine (r = 0.09). By contrast, the "Low" NPT group shows no correlation between maximum NPT and maximum response to erotic stimuli (r = 0.05) but correlates better with maximum response after injection (r = 0.41, $P = 0.057$).

Psychometric measures

The mean scores for the GRISS and its subscales, the 4 scales of the SES, and the Locke–Wallace Marital Adjustment Scale for the High and Low NPT groups are shown in Table 6. There are no differences between the 2 groups at the 5% level, but 2 trends. Thus the low NPT group have a higher (*i.e.* more restrictive) score for sexual morality (SES1, $P = 0.06$) and higher (*i.e.* more avoiding) score for psychosexual stimulation (SES2, $P = 0.09$).

Subjects were also divided according to their maximum response to erotic stimuli before papaverine, again using the best median split. As 4 men did not complete the psychometric tests, this resulted in 17 in the "low" and 21 in the "high" group. Comparison of these 2 groups for the

Table 6 Psychometric Measures for Low and High NPT Groups

	Low NPT		*High NPT*		
Scale	*n*	*Mean (s.d.)*	*n*	*Mean (s.d.)*	*P*
GRISS:					
Overall	18	7.2 (1.5)	20	6.9 (1.7)	n.s.
Impotence	18	6.6 (1.1)	20	6.8 (1.8)	n.s.
Premature Ejaculation	18	6.4 (1.8)	20	5.4 (2.3)	n.s.
Male Non-sensuality	18	1.2 (0.5)	20	1.0 (0.2)	n.s.
Male Avoidance	18	3.1 (2.3)	20	3.5 (2.2)	n.s
Male Dissatisfaction	18	3.7 (1.8)	20	3.8 (2.1)	n.s.
Infrequency	18	6.7 (1.9)	20	6.6 (1.5)	n.s.
Non-communication	18	4.8 (1.7)	20	4.0 (1.8)	n.s.
SES-1: Sexual Morality Scale	19	60.3 (12.1)	19	51.9 (14.3)	0.06
SES-2: Psychosexual Stimulation Scale	19	43.5 (10.9)	19	37.9 (9.1)	0.09
SES-4: Attraction to Marriage Scale	18	69.1 (13.1)	17	66.6 (11.8)	n.s.
SES-3: Sexual Motivation Scale	18	64.4 (18.0)	19	66.0 (14.9)	n.s.
Locke–Wallace Marital Adjustment Scale	17	118.5 (22.9)	17	104.5 (27.6)	n.s.

psychometric variables showed no differences that approached significance.

Of interest are the subjects who showed low correlation between their NPT and their response to erotic stimuli and papaverine. A 2 × 2 ANOVA was therefore carried out for each of the psychometric variables, comparing the 4 groups: "high" on both measures, "low" on both measures, "high" NPT and "low" erotic, "low" NPT and "high" erotic. There were no significant interactions for any of the variables. Thus we were not able to identify any distinguishing psychometric characteristics of those whose reponses during sleep and to erotic stimuli were inconsistent.

Age

The only NPT variable to correlate with age was "time above 5 mm increase in diameter" ($r=-0.44$, $P=0.01$). Response to papaverine injection *per se* did not correlate with age, but maximum response to erotic stimuli prior to ICI showed a negative correlation ($r=-0.32$, $P=0.05$). Age also correlated with scales 1 and 2 of the Frenken SES (SES1 0.53, $P<0.01$; SES2 0.41, $P<0.01$). This showed that the older men had more restrictive sexual morality (SES1) and lower involvement in psychosexual stimulation (SES2). There was a positive correlation with the Locke–Wallace score ($r=0.36$, $P<0.05$), suggesting that the older men had more positive views of their marriages, and a positive correlation with the premature ejaculation score of the GRISS ($r=0.39$, $P<0.05$) which was not expected.

Clinical categorisation

The comparison of the 4 groups (*i.e.* "probable psychogenic", "probable vascular", "other organic" and "uncertain") for the parameters of erectile response is shown in Table 7. This shows the erectile response to erotic stimuli to be the best discriminator between the psychogenic group and the rest. This could, in part, reflect the age difference. Comparison of the SES scales showed the psychogenic group to be significantly less restrictive in terms of sexual morality (SES1), probably also reflecting the age difference. SES2 did not discriminate between groups. For SES3, the "Uncertain" group showed lower "psychosexual motivation" than both the vascular ($P=0.01$) and psychogenic ($P=0.04$) groups.

Discussion

Our first objective was to assess the value of the combination of VES and ICI. Although the design of this study does not allow a full comparison of this combination with either procedure used in isolation, some comparison is possible. We can compare the initial VES response with the VES response after ICI; and we can compare the first 10 minutes after the ICI with the subsequent combination of papaverine and VES. If we take the NPT response as the "diagnostic standard", then these results show that both response to visual erotic stimuli and response to papaverine discriminate between the "high" and "low" NPT groups. The response to papaverine alone (*i.e.* during first neutral stimulus) was only marginally better than the response to erotic stimuli alone. The best discrimination occurred with the combination of the two. The value of the visual erotic stimuli may be greatest in younger men, as response to such

Table 7 Comparison of Erectile Parameters for 4 Clinical Categories (Means and Standard Deviations)

	Probable Psychogenic (n=12)	*Probable Vascular (n=11)*	*Other Organic (n=8)*	*Uncertain (n=12)*	*F ratio df 3, 38*
Max. NPT (mm increase diameter)	11.9 (4.9)	8.5 (4.4)	9.1 (6.5)	7.3* (5.6)	n.s.
Max. response to erotic stimuli ((mm increase diameter)	7.4 (4.6)	3.2† (2.9)	3.9* (4.6)	3.7† (3.0)	F=3.01 *P*=0.04
Max. response to papaverine alone after 10 min (mm increase diameter)	5.2 (4.3)	4.0 (1.7)	3.4 (2.5)	3.3 (2.2)	n.s.
Max. response to papaverine plus erotic stimulus	10.4 (4.7)	6.8§ (3.6)	9.0 (7.0)	6.2* (3.6)	n.s.

Comparison with psychogenic group (*t*-test): § $P=0.07$ * $P<0.05$ † $P<0.025$

stimuli was negatively correlated with age. It is therefore possible that a combination of low dose papaverine and VES would reduce the need for high dose papaverine, the repeated injections that result and the increased risk of prolonged erection. The development of drug combinations with greater potency but low risk of prolonged erection might permit reliance on single testing without VES and would be a considerable advantage.

Our second objective was to explore the relationship between these 3 methods of assessment. Although there is clearly a degree of overlap between them, there are also substantial differences which require explanation if such methods are to have high clinical diagnostic value. Let us first consider other relevant evidence.

In 3 previous studies using a combination of NPT and visual erotic stimuli (but not papaverine) the results can be summarised as follows. Zuckerman *et al.* (1985) compared diabetic and non-diabetic dysfunctional men and controls. They found that the 2 dysfunctional groups did not differ significantly from each other in their response to erotic stimuli, but did so in the NPT responses, the non-diabetic (and presumably more psychogenic) group showing higher NPT. Wincze *et al.* (1988) divided their 61 men into 4 groups: (a) no dysfunction, (b) vasculogenic dysfunction, (c) "high risk" dysfunctional men, who in spite of associated disease (*e.g.* diabetes) had no objective evidence of organic damage (*e.g.* Penile Blood Pressure Index or Sacral Evoked Response), and (d) psychogenic dysfunction. They found that their vasculogenic group showed greater erectile response to the erotic stimuli than during sleep (though both responses were usually low). They also divided their psychogenic group into 2 distinct subgroups, one of which produced virtually normal responses to erotic stimuli, while the other responded very poorly. Unfortunately, they had no systematic assessment of psychological factors that might have accounted for this distinction. In an earlier study of 31 men (Bancroft, 1984), we found that of 17 men, both dysfunctional and controls, who produced a mean erectile response to erotic stimuli greater than 5 mm increase in diameter, all but 1 produced maximum NPT responses also greater than 5 mm. Of the 14 subjects whose mean response to erotic stimuli was less than 5 mm (only dysfunctional subjects), 7 produced at least one NPT response greater than 5 mm.

Some caution is required in drawing comparisons across these studies, however. In the study reported here, the maximum erection during sleep was substantially greater than those occurring in response to erotic stimuli, in both the "high" and "low" NPT groups. In the "high" NPT group it was even greater than the maximum response obtained after the combination of papaverine 30 mg and erotic stimuli; in the "low" NPT group this was not the case. It is to be expected that response to erotic stimuli will be relatively inhibited compared with response during sleep, especially in men with erectile dysfunction. It is more surprising to find that this dose of intracavernosal papaverine, particularly when combined with erotic stimulation, does not eliminate this discrepancy. In nearly all cases, this injection of papaverine was the first intracavernosal injection experienced. As such, it would not be surprising if the anticipation of this injection inhibited the initial response to the erotic stimulus. Buvat *et al.* (1990) have pointed out the potential for impairment of response to intracavernosal drugs by psychological inhibition. Responses may therefore have been generally greater, if the subjects had already experienced intracavernosal injection. In an earlier study (Bancroft *et al.*, 1985) which compared 19 diabetic and 19 non-diabetic men with erectile dysfunction with 19 controls, we used similar procedures and similar erotic films without involving intracavernosal injections. Combining the 2 dysfunctional groups we found a mean maximum response to erotic films of 6.2 mm increase in diameter; this compares with an overall mean of 3.1 in this study. This would support the view that the injection had an inhibiting effect. However, in the 2 other studies cited here, the overall mean response to erotic films for the dysfunctional men was only 1 mm increase in diameter for Zuckerman *et al.* (1985); and 2.5 mm increase in diameter for Wincze *et al.* (1988). Thus there may be other factors, including type of film material, varying subject characteristics and variations in procedure, which could account for these variable responses. It should also be pointed out that there are considerable differences between studies in the mean NPT response, as well as the level of NPT which is regarded as normal. Thus the overall mean maximum increase in penile diameter during NPT in this study was 7.6 mm. In the Zuckerman *et al.* (1985) study it was 4.6 mm, and in the Wincze *et al.* (1988) 2.9 mm. The latter authors regarded a 4.5 mm increase in diameter (*i.e.* 15 mm increase in circumference) as indicative of a fully functional erection. In our experience, a full erection (regardless of rigidity) is seldom less than 10 mm increase in diameter and Buvat *et al.* (1990) in their comprehensive review, concluded that 7.5 mm (25 mm circumference) was a minimum for diagnosing a "normal" or "psychogenic" NPT.

There is also limited evidence relating NPT to response to ICI. Buvat *et al.* (1990) summarised their findings in 80 men who received both procedures and substantially higher papaverine dosage than employed in our study. Of 25 cases with "normal" NPT only 11 had a full response to 80 mg of papaverine. Of the 55 with "abnormal" NPT, 8 produced full and 9 partial responses to 80 mg papaverine. They concluded that negative responses to ICI were not unusual in psychogenic cases, and suggested that fear-induced increase in adrenergic tone, invoked by the injection, might be responsible. Such a reaction, whatever the precise autonomic mechanism involved, could be an important aspect of *some* types of psychogenic dysfunction. This is consistent with the variable correlation between NPT and response to ICI in our "high" NPT group.

In this study, for assessing maximum erectile capacity, NPT appeared best, although it should be remembered that, for comparison, we used a low dose of papaverine. We did not measure sleep parameters in this study, and possibly a few of our subjects would have been excluded on the grounds of inadequate sleep. However, the clinical application of NPT is much greater if it can be usefully measured without sleep recording, which is prohibitively expensive. We found further evidence of a first night effect, although mainly in duration of response greater than 5 mm increase in diameter (16 mm increase in circumference) not in the parameters of NPT that are usually emphasised (*e.g.* maximum response). We were not able, in this study, to measure rigidity. The diagnostic significance of different aspects of the NPT (*e.g.* maximum response, number, duration and rigidity of response) have not as yet been adequately investigated. The clinical value of NPT is increasingly questioned (*e.g.* Buvat *et al.*, 1990) but, we believe, may be clarified if greater research attention is paid to the diagnostic significance of these different parameters.

In the low NPT group, the papaverine plus erotic stimulus produced slightly greater erectile response than the NPT, and the 2 responses were correlated. The response to the erotic stimulus alone, in this group, was disappointing and was poorly correlated with NPT, probably because of its generally low level, giving us little diagnostic information. In such men, therefore, the use of either NPT or papaverine (preferably combined with VES) is of comparable diagnostic value. The use of higher dosage of papaverine might be indicated in this group.

In the "High" NPT group, the situation is more complex. The response to erotic stimuli is better and correlates to some extent with maximum NPT. Response after papaverine, however, shows no correlation with NPT. This is an interesting difference requiring explanation. Something happens as a result of the injection which alters the responsiveness in a variable way in these men, thus eliminating any correlation with the NPT. Is there a psychological explanation for this effect, at least in part? It is possible that in this group, who are likely to be mainly psychogenic, there are some for whom anxiety about the injection impairs the response to the papaverine. Careful study is required of the psychological reactions to the intracavernosal injection and their relation to the erectile response.

Our third objective was to examine the relationship between these 3 measures and our diagnostic groupings based on routine clinical examination and sexual and medical history. We were unable to replicate the findings of Wincze *et al.* (1988) that men with vasculogenic dysfunction produced better responses to visual erotic stimuli than during sleep. Our success in discriminating between our clinical categories was also limited; the principal differences, between the "probable psychogenic" and the other 3 categories, could be largely accounted for by the age differences. Better discrimination might have been achieved if our categorisation had been based on more objective methods of assessing vascular or neurological pathology. However, it remains a clinically important question to establish how much these specialised techniques, which are not widely available, add to a careful clinical and sexual history. Further work is required in which more systematically collected clinical information is compared with the measures reported in this paper.

Our failure to find any psychometric correlate of response to the methods of assessing erectile function is disappointing but should not lead us to abandon such an approach. Our attempt was crude, and further studies should use more precisely formulated questions with appropriate methods of measurement, *e.g.* to assess psychological reaction to the intracavernosal injection or the erotic stimuli.

Much of the existing confusion in the literature stems from the assumption that erectile dysfunction can be dichotomised into "organic" and "psychogenic". Human sexuality is an essentially psychosomatic process (Bancroft, 1990) and such a distinction is seldom appropriate or helpful. We should rather be assessing the relative importance of different types of aetiological mechanisms. Also it is clearly too simplistic to see these 3 methods of assessment as alternatives. Different mechanisms are likely to be involved in each case, and will vary in their aetiological importance. We have already shown, in studies of androgen deficiency and replacement, that erectile response to erotic stimuli differs in important ways from NPT (Bancroft and Wu, 1983; O'Carroll *et al.*, 1985). The second is clearly androgen dependent; the first is not. This led to the hypothesis that there are at least 2 systems in the brain underlying erectile response. One is androgen dependent, linked to sexual desire and manifested physiologically as NPT. Measurement of these spontaneous erections during sleep therefore provides a window into this neurophysiological substrate of central arousability. The other system responds to certain types of external stimuli, in particular visual. We should therefore expect there to be differences in the factors affecting these 2 kinds of response, beyond the fact that in one situation the person is awake and hence subject to psychological influences, to which the sleeping person is not.

The intracavernosal injection of smooth muscle relaxant drugs raises yet further factors influencing response. On the one hand there is the potential for direct drug effects on the peripheral vascular mechanisms underlying erection. It is clearly this effect that has captured the imagination of clinicians using this method, most of whom see this as free from the complicating effects of the psyche. Although they were exceptions, the 4 men whose response to erotic stimuli was substantially enhanced by the papaverine are of potential interest. It is possible in their case that the peripherally administered drug was modulating a centrally mediated erectile response. Such an effect may be particularly relevant in the presence of partial neurogenic failure. In addition, it looks increasingly likely that psychological mechanisms can inhibit such pharmacological responses, and an understanding of such mechanisms may throw considerable light onto the persistently obscure nature of psychogenic erectile failure.

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The Importance of the Leak Point

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Until recently, in the case of infants with spina bifida, nature was left to take its course, which usually resulted in death from ascending infection or progressive hydrocephalus. Antibiotics, reconstructive surgical techniques and effective ventricular shunts in the 1950s created a population of surviving children with myelodysplasia. One of the main threats to life became that of renal failure.

Surgeons recognised that renal failure was preceded by bladder dysfunction and ileal conduit urinary diversion was performed extensively in the 1960s. The introduction of the principle of clean intermittent catheterisation by Lapides in 1971 provided a preferable alternative to urinary diversion and was also the key that unlocked the door to bladder reconstruction and undiversion.

McGuire's leak point concept in 1983 linked upper tract deterioration to high bladder pressures. This very practical urodynamic measurement can be made by a simple catheter and manometer. If bladder storage pressures are less than 40 cm H_2O, upper tract deterioration is unlikely, but if the pressures exceed that figure one can predict that progressive renal damage will occur.

Prolonged Bladder Pressure Monitoring in Children with Spina Bifida

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It has become a classical concept that in patients with spina bifida, bladder dysfunction can be the cause of impaired renal function over a period of time. McGuire states that deterioration occurs when the bladder pressure exceeds the critical value of 40 cm water. Values such as this, observed during urodynamic investigation, which is often an artificial situation with all too often excessively rapid bladder filling, raise the question as to how often such dangerously high pressures occur during the day and night and for how long they persist.

In a previous report we have shown a correlation between bladder volume at a pressure of 40 cm water and renal function. We measured the duration of high bladder pressure during a 12- or 24-h period of continuous monitoring in children who had shown high pressure peaks during standard urodynamic studies.

A total of 94 children with spina bifida of various levels had undergone standard urodynamic examination. Bladder filling was at 7 to 15 ml/min, depending on the age of the patient. Bladder and rectal pressures were measured with Gaeltec microtip pressure sensors; sphincter EMG was recorded with coaxial electrodes. Nine children above 3 years of age showed more than 40 cm water pressure in the bladder at volumes of less than normal values for their age. They then underwent continuous pressure measurement by means of the Krypton Urodym system, which consists of a 4-channel computerised recording of bladder and rectal pressures, integrated perineal EMG and, in girls, distal urethral conductance.

The portable system has a microprocessor which simultaneously records 3 or 4 valves which are automatically rejected whilst the bladder pressure remains stable. Only changes in pressure are recorded.

In patients who showed high bladder pressure during repeated uninhibited bladder contractions, or those with low compliance but with pressure plateaus, the duration of high pressure during 12/24-h monitoring lasted from 45 min to 7.5 h. Some showed intermittent high pressures and others long-lasting high pressures. After taking account of a maximum of 10 voids a day, each lasting for 15 s, the normal duration of high pressure was less than 3 min/day. This study suggests that some children with spina bifida surpass these values. Their vesicourethral junctions are submitted to prolonged strong pressures which in turn could adversely affect the upper tracts and hence renal function. The study confirms the need to treat this condition vigorously.

The Changing Pattern of Cystometry in Infants with Myelomeningocele

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The neurogenic disturbance of bladder function seen in infants with myelomeningocele (MMC) shows a wide variation of detrusor and sphincter responses. By repeating cystometry 3 times during the first year of life we wished to elucidate whether these responses changed with time and whether we could recognise patterns with potential deleterious effects on the upper urinary tract.

Between 1986 and 1989 we investigated 31 infants (14 boys and 17 girls) with cystometry and uroradiology at the age of 1, 4 and 10 months respectively.

At the first examination (1 month of age) 18 children had a more or less stable detrusor during filling and of these infants 10 had a normal detrusor contraction during emptying. The remaining 13 infants had different grades of hyper-reflexia during filling; 5 of these latter babies had a leakage pressure above 60 cm H_2O, indicating severe dyssynergia, whereas another 5 had a leakage pressure below 40 cm H_2O, indicating sphincter weakness.

At the age of 4 months, 6 of the 17 patients with a stable detrusor during filling had developed a moderate grade of hyper-reflexia, whereas all patients with severe hyper-reflexia at the age of 1 month remained unchanged.

From 4 to 10 months the pattern remained mainly unchanged.

The cystometric pattern changed in some of the infants with MMC during the first year of life, especially between the 1st and the 4th month of age, from a pattern of areflexia of the detrusor to moderate grades of hyper-reflexia. Furthermore, it seems possible to identify the high risk group from the first month of life, since the cystometric pattern in babies with severe hyper-reflexia and dyssynergia remained unchanged.

Spinal Dysraphism and Neurological Bladder

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A retrospective study was made of the urological symptoms of 133 patients with spinal dysraphism other than meningomyelocele. They were all treated before 1987, giving a 3-year follow-up. Four patients who died, 10 who were lost to follow-up and 17 with minor spinal dysraphism such as dermal sinuses were excluded.

There were 56 cases of sacral agenesis, 64 with tethered cord, 58 with spinal lipoma, 14 with diastematomyelia, 5 with medullary hypoplasia, 5 with enterogenous cyst and 4 with meningeal cyst. Six groups were analysed for the urological symptoms which led to the diagnosis of spinal dysraphism and the urological complications thereafter They were grouped as follows: 25 with sacral agenesis, tethered cord or lipoma, 33 with tethered cord and lipoma, 6 with sacral agenesis and tethered cord, 25 with sacral agenesis only, 7 with a dermal sinus only and 6 with various malformations.

Amongst the series of 44 males and 58 females, urological symptoms led to the diagnosis in 25.4% of cases Urological complications occurred in 51.9% and 4.9% suffered urological sequelae such as diversion, nephrectomy or renal failure. The diagnosis was made during the first year of life in 40% but in 5.8% the diagnosis was made only after poor results following urinary tract surgery.

Tethered Cord and Urodynamic Changes in Children with Myelomeningocele

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Magnetic resonance (MR) is helpful in the follow-up of myelomeningocele (MMC) patients; the finding of a "tethered cord" raised the question of whether these patients should or should not undergo a second-look laminectomy

Of 154 MMC patients seen at this institution, 40 (45%) have been followed up since birth; 34 of them were investigated by means of sacral MR and followed up urodynamically. Seventeen have had a complete urodynamic follow-up.

Five of these 17 children had severe "tethering" (group A) and 12 only mild or moderate "tethering" (group B). Urodynamic patterns had changed in 6 cases (35%), that is the same percentage of urodynamic changes in all MMC patients followed up since birth.

Comparing the grade of "tethering" with the urodynamic pattern, detrusor activity has modified in 2 group A patients (48%) and 4 group B patients (33%). In both children in group A and in 2 in group B, previous hyper-reflexia changed into areflexia. In the remaining 2 children in group B, the previously areflexic detrusor became hyper-reflexic.

The urodynamic variability does not seem to be correlated to the morphological severity of the tethered cord found at MR. Therefore, further prospective combined morphological and functional (urodynamic and neurophysiological) studies are necessary in order to define which patients with MMC should be considered for neurosurgical revision.

Changes in Urodynamic Findings in Children with Tethered Spinal Cord Syndrome due to Surgical Untethering Procedures

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The tethered spinal cord syndrome (TSCS) is characterised by a pathological fixation of the cord to an abnormal caudal position caused by a tethered filum terminale, by miscellaneous dysraphic entities or following surgical repair of meningomyelocele (MMC). With growth, mechanical stretching may result in an ischaemia of the cord leading to progressive neurological deficits. Surgical intervention may prevent or improve these neurological symptoms. Neurogenic bladder dysfunction may be one of these progressive deficits in TSCS but may also develop with or after neurosurgical intervention.

We compared the pre- and post-operative bladder function in 12 children and adolescents presenting with TSCS in order to determine the changes in bladder function following tethered cord release. The patients were 1 to 18 years old. The majority of TSCS was due to previous surgery for MMC. Pre-operatively, a neurogenic bladder dysfunction was found in 8 patients, 3 of them presenting without any clinical sign of bladder dysfunction. Post-operatively, a transient amelioration of bladder dysfunction was seen in only 3 patients with a hyperreflexive detrusor function; normal bladder function was never achieved. Two children developed urinary retention requiring intermittent catheterisation, one of them having had no voiding abnormalities before, although minor urodynamic signs of overactive detrusor function were present when the child was urodynamically examined pre-operatively.

These data demonstrate a significant incidence of neurogenic bladder dysfunction in patients with TSCS. Changes in bladder function occur following surgical release of the tethered cord, showing a deterioration of bladder function in at least 2 of our patients. We therefore regard urodynamic evaluation as essential in the pre- and post-operative period in patients with tethered spinal cord syndrome.

The Management of the Neuropathic Bladder in Adolescents with Imperforate Anus

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The management of 58 patients born with imperforate anus presenting to the urology service, and who are now 18 years or older, is discussed. The "high" anomaly was treated by a rectal pull-through in 43 children, the "low" anomaly treated by an anal cut-back in 14 children; 32 children (55%) had a neuropathic bladder, being hyperreflexic in 29 cases and atonic in 3. Spinal deformity was present in 72% of the hyper-reflexic group but was not present in the atonic group.

Vesicoureteric reflux occurred in 41% of cases, two-thirds of which had a neuropathic bladder, 30 children had an associated genital anomaly, 27 children an upper tract anomaly.

Nineteen children had operative management of their neuropathic bladder, it being clear that modern reconstructive methods involving substitution or augmentation cystoplasty, supplemented with self-catheterisation, are superior to older methods with regard to continence.

The incidence of neuropathic bladder in these children is high in both operative groups but is usually associated with a spinal deformity and unlikely to be iatrogenic in nature, unless proven to be of lower motor neurone origin. Early operative management is advised to achieve continence and minimise renal impairment.

Urodynamic Investigations in Children with the Caudal Regression Syndrome

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The caudal regression syndrome (CRS) represents a wide spectrum of somatic and visceral abnormalities, including the lower limbs, the lumbosacral spine, the anorectum and the genitourinary tract. Lower urinary tract dysfunction is common in these children and related to anatomical or functional causes. Functional voiding disorders are generally due to neurogenic bladder/sphincter dysfunction on the basis of lumbosacral dysgenesis or tethering of the spinal cord. Therefore we began to evaluate these children routinely by standard urodynamic investigations (UDI).

Since 1976 we were able to evaluate 50 children comprehensively, 31 boys and 19 girls; 20 (40%) had more than one UDI. Mean age at first UDI was 40 months (range 1–176); 15 children had sacral agenesis (SA) only; 13 had SA and anorectal malformations (AM) and 22 had AM only, with no sacral defects. In all, 24 children (48%) had associated genitourinary anomalies, 15 (30%) had reflux and 5 (10%) had a proven tethered cord (TC). Neurogenic bladder/sphincter dysfunction (NBSD) was found in 11 children with SA alone and in 10 children with combined SA and AM; 4 children with AM only had lower urinary tract dysfunction. Of these, 1 child had posterior urethral valves, 1 was thought to have NBSD and 2 had idiopathic detrusor instability, 31% (n = 11) of the children with AM had NBSD, of whom 10 had total or partial SA; 75% (n = 21) of the children with SA had neurogenic dysfunction, whether they had or did not have AM. Though 4 of these children had a tethered cord, the exact cause of NBSD in the other children was not clear; 7 children had UDI before and after posterior sagittal anorectoplasty (PSARP), with no change in the urodynamic pattern. Therefore PSARP seems to have no influence on bladder/sphincter function. It was concluded that all children with features of CRS should have urodynamic evaluation.

Sacral Anterior Root Stimulator Implants in the Management of Neurogenic Bladder Disorders in Adolescents

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Sacral anterior root stimulator implants were first used in the management of neurogenic bladder disorders in adults with spinal cord injuries in 1978, and the number implanted per year has steadily increased over the period

1983–1990. In conjunction with sacral posterior rhizotomy, they abolish reflex incontinence, improve bladder compliance, reduce residual urine volumes and bring voiding pressures under control.

Only a few adolescents have been treated, and no children aged less than 14. It is recommended that many more adolescents, with meningomyelocele as well as with spinal cord injuries, could benefit from this treatment.

Nine Years' Experience with Clean Intermittent Catheterisation in Children with Neuropathic Incontinence

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The state of urinary continence, renal function, upper tracts and urinary infection was assessed in 29 children with neuropathic bladder, who had been managed by a programme of 4-hourly clean intermittent catheterisation (CIC) between 1982 and 1990. There were 13 boys and 16 girls, aged 1 month to 16 years (mean 9 years). The cause of bladder dysfunction was myelomeningocele in 20 patients, sacral agenesis in 3, functional (occult) bladder-sphincter dyssynergia in 5 and myelitis in 1. Mean age at institution of CIC was 5 years and follow-up extended from 1 to 9 years (mean 6.5). All patients had been totally incontinent prior to CIC. Three patients did not comply and discontinued CIC; of 26 patients still undergoing CIC, 23 were completely dry, whilst 2 more were dry at 3 hours. In 12 of these patients complementary pharmacological manipulation was necessary to control hyper-reflexia and/or dyssynergia, and in 1 bladder augmentation had to be performed. CIC failed to control incontinence in only 1 patient who had intractable hyper-reflexia. Five patients had raised plasma creatinine (>150 μmol/l) before CIC; in all of them kidney function was normal at the end of follow-up. Vesicoureteric reflux (>grade III) was noted in 13 ureters prior to CIC and hydronephrosis in 2 more renal units. Following CIC, reflux resolved in 5 ureters and substantially improved in 2 more (grade I), whereas hydronephrosis disappeared in both renal units. Finally, the incidence of symptomatic urinary infections was reduced from 1 episode/patient/month to 1 episode/patient/year. The evidence from this survey shows that CIC was effective in controlling neuropathic incontinence, helped to stabilise renal function, cured vesicoureteric reflux in more than 50% of the cases and virtually eliminated symptomatic urinary tract infections. For this reason it should be offered as a primary option in the management of children with neuropathic incontinence, alone or in combination with appropriate pharmacological agents.

Clean Intermittent Catheterisation in Myelomeningocele: Effects on Urinary Infection and Incontinence

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In children with myelomeningocele (MMC) many urinary tract infections (UTI) will be complicated, belonging to the realm of obstructive uropathy. UTI in children with MMC can go untreated for a long time, because of lack of specific symptoms; obstruction and chronic undetected infection not only cause progressive renal scarring, they also convert the bladder wall into a non-compliant, small-capacity fibrotic structure, with continuously high pressures imposing further damage on the already compromised upper urinary tracts.

With clean intermittent (self) catheterisation (CIC), a simple alternative became available for relief of functional infravesical obstruction. Although the primary objective of CIC was to regain continence in (older) children with MMC, we decided to use it also in the very young with detrusor-sphincter dyssynergia, to prevent future damage from the combined effects of obstruction and infection. The results, in terms of incidence of UTI and degree of incontinence before and during CIC, were assessed with a questionnaire mailed to 61 consecutive children with MMC who had started CIC between 1985 and 1988; 55 questionnaires were returned, all correctly filled out (response rate 90%). Mean follow-up was 45 ± 26 months; mean age at the start of CIC was 7.1 ± 4.6 years.

With Cochran's χ^2 test, the incidence of UTI during CIC proved significantly lower than before CIC ($\chi^2 = 20.92$, $P < 0.001$) and the improvement in incontinence was also statistically significant ($\chi^2 = 45.16$, $P < 0.001$).

In children with MMC, CIC seems ideally suited to prevent damage to kidneys and bladder wall from the life-long problem of recurrent UTI; residual urine and retention are prevented, colony counts of urine samples at regular intervals can be carried out effectively, and the responsibility for treatment and monitoring is shared.

Long-term Study of Clean Intermittent Catheterisation in the Management of Neuropathic Bladder

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We have reviewed the results of 192 patients using clean intermittent catheterisation (CIC) who were seen at Addenbrooke's Hospital, Cambridge, since 1975. Of these, 70 had started CIC in childhood (aged 5 weeks to 16 years). Only 2 patients have shown deterioration in the upper urinary tracts. Urinary infections were not a problem but some patients with pre-existing renal damage (scarring and hydronephrosis) showed a significantly higher incidence of infections with *Klebsiella*, *Proteus* and *Pseudomonas* groups of organisms as well as having a higher degree of pyuria.

When reviewed, 70% were still using CIC and the majority managed independently. Those who remained dependent were either quite young, had severe spinal deformity, were blind or mentally retarded. Reasons for discontinuing CIC reflected the patient's preference or that of the carer. Six preferred to have an indwelling catheter. Satisfactory control, without catheterisation, was achieved by 6 patients, one of whom had a bladder augmentation. One patient subsequently had a urinary diversion.

There were no deaths from renal failure amongst the patients using CIC despite the preponderance (82%) of cases of myelomeningocele. There were, however, 10 deaths from renal failure amongst the patients with myelomeningocele who were not on CIC during the period of this review. The safety of the method depends on effective urinary drainage; to prevent bladder overfilling, catheterisation must be performed at least 4 times a day.

Prophylactic Use of Intermittent Catheterisation in Children with Spina Bifida

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Although clean intermittent catheterisation (CIC) is a critical ingredient in the optimum management of many children with neurogenic bladder, the precise indication and time for starting CIC remain controversial. Many centres adopt an expectant approach and start CIC only after signs of upper tract deterioration appear, such as hydronephrosis or renal scarring. In 1982, we began a protocol for instituting CIC prophylactically in infants and young children with spina bifida whenever urodynamic studies demonstrated prognostically unfavourable patterns. Preliminary results indicated that prophylactic institution of CIC based on urodynamic findings significantly reduced the likelihood of urinary tract deterioration. We have since noted that many patients develop changing urodynamic patterns and that clinical deterioration may ensue before urodynamic reassessment. Clinical signs of urodynamic change include impaired bladder emptying and recurrent episodes of bacteriuria. This has led us to expand our criteria for prophylactic CIC to include these conditions.

To date we have started CIC prophylactically in 38 patients with spina bifida followed up for 4 years (average) and can compare them with 66 non-prophylactically managed children. Results show that prophylactic CIC reduced the likelihood of upper tract deterioration from 35 to 10% and confirm that a larger population of children are at risk of deterioration than can be detected by periodic urodynamic study. We conclude that using CIC to prevent rather than to treat urinary tract disease is the management of choice for children with spina bifida and that urodynamic criteria alone are insufficient to identify all patients at risk.

Therapeutic Management of Children with Myelomeningocele

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The management of neurogenic bladder dysfunction in children with myelomeningocele aims to preserve renal function and prevent incontinence. Of 320 children, 80% showed a spastic bladder and 20% a flaccid bladder. Until 1985 the primary therapeutic concept was to lower the bladder outlet resistance in order to protect renal function, accepting complete incontinence. Since then we have followed a new strategy, taking the problem of incontinence equally into account. It was necessary to evaluate whether continence affects renal function. All children were treated with dibenzyran (0.5 mg/kg) from birth until the age of 5 years, after which medication was stopped. After urodynamic assessment, children with a spastic bladder were treated with oxybutynin 2.5 mg 3 times a day. All children were treated with clean intermittent catheterisation.

Children showing reflux or recurrent urinary tract infections received chemoprophylaxis; 90 children have so far been treated in this manner. In 80%, urinary continence with dry periods of at least 3 h was achieved; 10% had shorter, but still satisfactory dry periods. Only 10% required an operation due to stress incontinence or inability to take drugs.

In the group of children treated before 1985, only 10% were continent. Furthermore, persistent residual urine, recurrent infections and a high intravesical pressure caused renal scarring in 15% (twice as many with reflux) of the children. None of the children treated since 1985 has shown evidence of renal damage. Thus continence can be achieved whilst renal function can be protected by means of sufficient spasmolytic medication and clean intermittent catheterisation.

Reconstruction of the Lower Urinary Tract for Neurogenic Bladder: Lessons from the Adolescent Age Group

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A total of 37 adolescents with neurogenic bladder have had reconstruction of the lower urinary tract. Preliminary investigation identified 3 other patients with severe spina bifida who were unfit for major surgery; 2 patients required post-operative respiratory intensive care. Sphincter competence and ability to self-catheterise (ICSC) were correctly predicted in 27 of 29 patients: they had bladder augmentations, 2 patients required artificial sphincters.

In 2 (of 24) female patients, excess residual bladder caused persistent hyper-reflexia. Three female patients developed painful bladder spasms with orgasm. They (20% of the female group) required excision of the residual bladder. The remaining 8 patients had continent urinary diversions. In 6 confined to wheelchairs the stoma was put in the epigastrium for ease of ICSC, 2 of them had major post-operative complications; 1 other patient was found dead in bed at home 6 months post-operatively from an unknown cause.

Lessons for childhood are: 1. Reconstruction in adolescence is a major operation. 2. If major bowel augmentation is to be done anyway, it might be better to remove the residual bladder. 3. Adolescents in wheelchairs are unlikely to be able to do ICSC on the urethra; they should have a continent diversion with a high abdominal stoma.

The Place of Autocystoplasty in the Management of the Neuropathic Bladder

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In order to create a low pressure reservoir of adequate capacity, a segment of intestine is customarily incorporated to augment the neuropathic bladder. This involves surgery of some magnitude. The long-term consequences include metabolic disorders, affecting bone metabolism and growth. Neoplasia or perforation of the intestinal segment is also reported. Of less gravity, mucus production may be a problem.

We report 11 children with neuropathic bladders, aged between 2½ and 14 years, in whom we have attempted to enlarge the bladder capacity without interposition of intestine. The detrusor muscle was divided extraperitoneally, leaving the urothelium intact, and allowing it to expand outwards as a large diverticulum.

The operation was uneventful and well tolerated. There were no major complications. Early cystoscopy showed an apparently normal mucosa. Follow-up ranges from 8 weeks to 18 months. Five patients reported an improvement in their continence and bladder capacity and 3 were unchanged. All had pre-operative urodynamic assessment and 5 were studied post-operatively. Two patients who reported no benefit had no change on urodynamic assessment; 3 patients who had clinical improvement showed a significant increase in the capacity of the bladder at the same detrusor pressure.

Biochemical surveys have also been conducted.

This early report suggests that autocystoplasty may have a place in the management of selected patients with neuropathic bladders.

Bladder Augmentation in Childhood. Is a Clam Cystoplasty Sufficient?

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Clam enterocystoplasty represents one of the simplest techniques for surgical bladder enlargement. In detrusor hyper-reflexia it is well established and in adults provides adequate clinical capacity. Its value in the fibrotic and non-compliant bladder has recently been challenged, and the concept of relating bladder volume to storage pressure is rarely emphasised.

A total of 23 children have undergone clam enterocystoplasty—17 with myelodysplasia and detrusor abnormality and 6 as part of a continent cutaneous diversion procedure in late ectopia vesicae. The length of ileal segment varied between 12 and 15 cm and the age range of the patients between 1.5 and 15 years.

In 21 patients slow fill cystometry was performed both pre- and post-operatively, with assessments made 6 months after surgery. Renographic and ultrasound assessment are performed in all patients, pre- and post-operatively, and 13 patients with myelodysplasia had hydronephrosis before treatment. All patients empty by clean intermittent self-catheterisation (CISC) 3- to 4-hourly.

The clinical results were as follows: 1. Bone-dry on 3- to 4-hourly CISC (15 of 23). 2. Dry with pad on 3- to 4-hourly CISC (5 of 23). 3. Clinical failure (3 of 23).

Failures were all due to inadequate pre-operative assessment of bladder neck competence and stress leakage occurs in all 3 patients.

Previous experience had led us to believe that pressures continuously above 20 cm of water are detrimental to long-term upper tract function. We believe that low pressure storage volume (LPSV) or functional bladder capacity should be described as that volume of urine stored at pressures below 20 cm of water. The urodynamic results are assessed on this basis. 1. LPSV created to accommodate safe 4-hourly CISC (mean 4-hourly CISC volume is <LPSV) (18 of 21). 2. High storage pressures at 4-hourly CISC (2 of 21). 3. Failure to create any increase in storage capacity (1 of 21).

It is concluded that clam cystoplasty using 12 to 15 cm segments of ileum to enlarge functional bladder capacity creates a satisfactory clinical and urodynamic situation in 80% of patients. Careful assessment of bladder neck competence is important in determining the post-operative result.

Metabolic Consequences of Enterocystoplasty

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A group of 106 children and adolescents underwent lower urinary tract reconstruction so that their urine is stored in a reservoir made in whole or in part from bowel. Types include augmentation and substitution cystoplasties, Kock and Mitrofanoff pouches. The intestinal segments are ileum in 28, colon in 71 and mixed in 7. Follow-up is 18 months to 12 years (mean 4 years).

Anaemia was found in 9 (none macrocytic).

Definite hyperchloraemic acidosis (HCA) was found in 14 and borderline results in a further 25 patients. HCA occurred mainly in patients with colonic reservoirs, but 2 definite and 8 borderline cases had purely ileal reservoirs.

Renal stones occurred in 5 and reservoir stones in 13, always associated with infection.

Delayed growth in height was found in 12 of 60 children (20%) who were appropriately measured, although growth in weight was maintained. This serious complication could not be attributed to any of the measured metabolic parameters.

Although reconstruction of the lower urinary tract with bowel is most satisfactory for neurogenic bladder, there is a high incidence of metabolic complications. Close follow-up is required.

Instability in the Augmented Neuropathic Bladder

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Some unstable neuropathic bladders demonstrate persistent post-operative instability despite generous augmentation with bowel. Cystometrographic tracings suggest that this activity may arise in the intestinal component of the augmented bladder.

From a total of 24 neuropathic bladder augmentations carried out personally on children between the ages of 2 and 18 years (mean 9.4), post-operative cystometrographic studies have been performed in 16. These have been compared with 70 studies in children with unaugmented unstable neuropathic bladders. The following criteria were used: 1. Bladder volume at first significant contraction. 2. Bladder volume at first urine leak. 3. Contraction frequency. 4. Maximal contraction amplitude. 5. Contraction duration. Statistical testing using analysis of variance showed a significant difference between pre- and post-augmentation recordings with respect to criteria 1, 3 and 4 and a marginally significant difference with respect to criterion 5.

The post-augmentation increase in bladder volume at first contraction is not surprising; this is what the operation aims to achieve. The leak volume is a property more of outflow resistance than muscular activity and would be expected to be the same before and after augmentation. The lower contraction frequency and amplitude and longer contraction duration is more characteristic of intestinal than vesical activity.

It is suggested that instability in the augmented neuropathic bladder may be due to activity in the intestinal segment. Thus dividing the bladder in more than one plane during augmentation will probably not influence post-operative spontaneous activity. In cases where there is marked detrusor hypertrophy it is more appropriate to perform a partial cystectomy.

Artificial Sphincter AS-800 in Children with Neurogenic Bladders

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The good results of the artificial sphincter (AS) in non-neurogenic incontinence have been well documented in many series, but for patients with neurogenic bladder the results seem disappointing. The aim of this report is to explain the difference.

Between June 1985 and September 1988, 16 children aged 9 to 17 years have had an AS implanted. All were incontinent (mostly with myelomeningocele) and had not improved with re-education. The mean follow-up was 38 months (range 22–63).

Continence was satisfactory in 9 children, half of them required anticholinergic medication and 3 underwent revision operations. In 2 children the AS was removed early because of urethral erosion or infection. Later it was removed 3 times: 1 urethral erosion 38 months after implantation and 2 upper tract deteriorations. Two children were incontinent: 1 has not achieved continence in spite of a secondary enterocystoplasty and the other is waiting for a revision operation.

Urodynamic analysis before and after implantation showed that bladders poorly compliant or with rhythmic contractions gave poor results. These urodynamic clues contraindicate AS implantation except when reversible with anticholinergic drugs or bladder occlusion test. Continence appeared to be independent of sphincter occlusion pressure; 94% of the bladders, even if the initial compliance was good, have deteriorated after reimplantation. If anticholinergic medication was not effective, either augmentation cystoplasty or external diversion was required. Bladder deterioration was not predictable by any means and cannot be specifically related to the AS Late deterioration occurred. Therefore a long follow-up is mandatory.

Strict selection of patients can lead to 70% success.

Urinary Artificial Sphincter in the Treatment of Incontinence in Adolescents with Spina Bifida

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From June 1982 to December 1990, 37 patients, aged between 13 and 19 years (35 M, 2 F), were treated for neurogenic urinary incontinence with an artificial sphincter.

All patients were treated with drugs pre-operatively. Transurethral sphincterotomy in boys and in females a bladder flap urethroplasty were carried out during the surgical procedure.

The cuff was placed at the bladder neck in 33 cases and at the urethral bulb in 4. The sphincter was activated about 3 weeks after implantation and after 2 months in 2 patients with associated bladder augmentation.

Operative and peri-operative complications occurred in 4 cases during the initial phase of the study. Later on we had to perform 19 post-operative operations because of mechanical problems.

A total of 33 patients are presently dry (90% success rate).

Post-operatively, normal upper urinary tracts were found in all patients except one, and none had significant urodynamic changes.

Scott's Artificial Urinary Sphincter in Children and Adolescents

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Structural or neurogenic incontinence may be a reservoir and/or a sphincter problem. In the latter group, patients need increased outflow resistance in order to become dry. The implantable prosthetic urinary sphincter developed by Brantley Scott is one way of achieving this.

Between 1981 and 1989, 35 patients (18 boys and 17 girls) were operated on, their mean age at surgery being 17 years (range 6–25). Indications for surgery were incontinence due to bladder dysfunction (NBD), bladder exstrophy (2 patients), epispadias (4) and fracture of the pelvis (2). All of the patients with NBD had tried clean intermittent catheterisation (CIC) without becoming acceptably dry. Two patients had previously been treated with free muscle transplants and 2 with a Young-Dees procedure.

Follow-up ranged from 8 months to 9 years. Of the 35 patients, 27 were dry or almost dry; 10 of these were on CIC and 2 on detrusor-relaxing drug treatment. Thirteen of the 27 patients had undergone a total of 28 re-operations; in 6 this was due to a cuff that was too large and in 22 it was due to malfunction of the device. In 3 patients the device functioned without problems for 1 to 2 years, after which time it had to be removed because of late exteriorisation of the cuff (? catheter damage). One patient had to be diverted because she refused CIC and developed serious kidney damage, and in 3 patients the device had to be removed because of an infection in connection with either the primary or the secondary operation. Six of these 7 patients have now undergone Kock or Mitrofanoff procedures.

The Scott prosthesis is an excellent alternative in certain selected patients with urinary incontinence. An adequate reservoir is the most important prerequisite. The operation is applicable to young children but the indications must be strictly defined and both patient and doctor must be prepared for further surgery and life-long follow-up.

Urinary Diversion via Continent Ileal Reservoir in Children and Adolescents

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Urinary diversion via the continent ileal reservoir (Kock pouch) was introduced clinically in the mid-1970s. Since then, this method and other later ones have gained wide acceptance as alternatives to conduit diversion. In 1987 the method was introduced in children and adolescents.

Between 1987 and 1990, 16 patients (8 boys and 8 girls) were operated on; their ages ranged from 13 to 24 years (mean 17). The diagnoses were myelomeningocele (10 patients), bladder exstrophy (3), sacral agenesis (1), bladder sarcoma (1) and bilateral reflux (1). Eleven patients had had previous diversions (8 Bricker procedures, 3 cutaneous ureterostomies) and the indications were either malfunction or the wish to avoid external appliances. In the other 5 patients the indications were intractable incontinence. All patients had been assessed and found unsuitable for undiversion and/or bladder augmentation. Attempts at clean intermittent catheterisation (CIC) and/or drug treatment had been unrewarding.

Follow-up ranged from 2 to 44 months (mean 21). Six weeks post-operatively 1 patient had a repeat laparotomy for intestinal adhesions. No other complications requiring surgical correction were encountered. Two patients experience minor irregular leakage, slightly wetting the pad over the stoma. All patients manage catheterisation well (4–5 times daily) despite mental retardation in a few patients. So far, no patient has shown progressive deterioration of renal function and/or metabolic complications.

The continent ileostomy is a reliable method with few complications and good functional results. It is an excellent method in children and adolescents where other methods (*e.g.* undiversion, bladder augmentation, CIC or drug treatment) are not suitable.

Continent Colonic Urinary Reservoir in Paediatric and Young Adult Patients with Neurogenic Bladder Disease

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Continent urinary reservoirs have replaced ileal and colonic conduits in many institutions to accomplish urinary diversion. We have continued to use the extended, detubularised right colonic segment (the Florida Pouch) as our choice for continent urinary diversion.

Eleven patients underwent the Florida Pouch procedure as an alternative for the management of complications secondary to neurogenic bladder disease. The aetiology of disease in these patients included myelomeningocele (7), traumatic/neurogenic (3) and tethered cord (1). Seven patients were converted from another type of diversion which included ileal conduit (6) and colon conduit (1). The average age was 22.2 years.

All patients presented adequate upper extremity dexterity. Ten patients are continent between catheterisation and none has experienced difficulty in catheterising the stoma. Metabolic complications included 1 patient with borderline acidosis requiring treatment and another patient with low serum red blood cells folic acid which has required treatment. None of the patients has developed chronic diarrhoea. The Florida Pouch procedure represents adequate treatment for the management of children and young adults with complications secondary to neurogenic bladder disease.

Continent Urinary Diversion using an Artificial Urinary Sphincter

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We report a new and simplified method of continent urinary diversion employing a modified AMS 800 artificial urinary sphincter. The cuff is placed just proximal to the stoma and the pump is replaced by an injection chamber located under the skin to allow for increasing the cuff pressure if necessary to obtain complete continence.

After first confirming the efficiency of the system in 3 dogs, the device was placed in 2 patients. The first had a neuropathic bladder treated initially by enterocystoplasty with an appendicocutaneous stoma. Secondary leakage was subsequently controlled by placement of the device with maintenance of an excellent result at 30 months. The second patient was a girl who had a urogenital rhabdomyosarcoma treated by anterior exenteration, radiotherapy and a sigmoid conduit diversion. This was subsequently converted to a continent reservoir by simple augmentation of the conduit and placement of the device with a good result being maintained at 20 months.

We believe these 2 cases illustrate the best indications for this procedure, namely primary or secondary leakage from a supposedly continent urinary diversion, and conversion of a freely draining conduit into a continent reservoir.

Long-term results are awaited, but our experience thus far encourages us to recommend this technique as a simple means of achieving a continent urinary diversion.

Vesicorenal Reflux in Neurogenic Bladder—Endoscopic Treatment with Bovine Collagen

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Neurogenic bladder dysfunction frequently generates vesicorenal reflux, resulting in upper urinary tract deterioration.

Persistence of significant vesicorenal reflux despite decompression of the lower urinary tract by intermittent catheterisation, anticholinergic and spasmolytic medication or cutaneous vesicostomy requires reflux correction to prevent recurrent upper urinary tract infection.

Surgical antireflux procedures in neurogenic bladders have an increased failure rate. The minimally invasive technique of endoscopic injection of a depot biomaterial submucosally at the ureteric orifice is effective for correction of reflux and can easily be repeated. Glutaraldehyde-cross-linked bovine collagen (Zyplast®) was used for endoscopic reflux correction in 8 children and adolescents with neurogenic bladder and persisting low pressure reflux grade 3 or 4. Seven patients had a myelomeningocele and 1 girl a post-traumatic paraplegia. Five girls and 3 boys with an age range of 1 to 17 years were treated. Bilateral reflux was found in 4 patients; in 2 cases reflux was associated with ureteric duplication.

Follow-up ranges from 8 months to 2 years. Cystography after 3 months revealed successful correction of reflux in 9 of 12 treated ureters. A second collagen injection was given in 3 ureters after 9 and 12 months respectively. No adverse effects were encountered.

In combination with strict measures of lower urinary tract decompression, endoscopic treatment of reflux by submucosal collagen injection was effective and safe. Even in cases of recurrence of reflux, the frequency of urinary tract infections had decreased.

Results of Treatment of Vesicoureteric Reflux in Neurogenic Bladders

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A total of 641 patients with neurogenic bladders were observed between 1980 and 1989 in 6 Italian Departments of Paediatric Surgery; of these, 74 (16%) were due to spina bifida. Reflux (VUR) was detected in 199 patients (32.5%). Details of treatment and follow-up were available in 170 cases. Primary conservative medical treatment was chosen in 127 patients (76%): 121 were treated with clean intermittent catheterisation (CIC) and anticholinergics, 2 with antibiotics only, 1 with scheduled micturition, 1 with urethral dilatation and 2 received no treatment.

The results of conservative therapy were as follows: VUR disappeared in 60 patients and lessened in 11 (55.8%), was unchanged in 17 (13%) and worsened in 36

(28.5%); 13 patients were subsequently treated surgically. Primary surgical treatment was chosen in 43 patients (24%): 37 ureteric reimplants, 27 simple, 8 in association with bladder augmentation and 2 with a cystostomy, and 6 cystostomies. After surgery most of the patients undertook clean intermittent catheterisation. The results of surgical treatment were as follows: VUR ceased in 35 patients (81%), lessened in 3 (6.9%), was unchanged in 3 and worsened in 2. Further surgery was performed in 15 patients (13 after failure of conservative treatment and 2 after surgical failures).

Of these, 14 ureteric reimplants have been performed: 8 simple and 6 with bladder augmentation, in the last case, an ileal substitution was used for a sloughed ureter. The results of secondary surgery have been satisfactory. Correct urodynamic diagnosis and strict observation of therapeutic regimens are necessary for satisfactory results.

The Antegrade Continence Enema—An Adaptation of the Mitrofanoff Principle. A New Approach to Faecal Incontinence

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Chronic intractable faecal incontinence is commonly found in patients with neuropathic bladder Traditionally the management of both forms of incontinence has been separate, very often with 2 different specialties involved. Recent operative developments have now made this division artificial and we can no longer consider the management of either form of incontinence in isolation. We describe a novel operative approach to faecal incontinence and discuss its implications for the urologist. Total antegrade colonic irrigation is well recognised as a useful technique for pre-operative and "on the table" colonic preparation. A similar approach could be used in chronic faecal incontinence if a method of delivering the antegrade washout were available. A submucosal reimplantation of the appendix into the caecum would create a non-refluxing catheterisable channel that could be brought out on to the abdominal wall as a continent stoma (the Mitrofanoff principle) and thus provide access for an antegrade enema. The technique has now been successfully applied in 10 patients, 4 of whom underwent simultaneous lower urinary tract reconstruction for urinary incontinence. The operative procedures and post-operative management regimes are described in detail. It is hoped that the introduction of the antegrade continence enema will avert the need for permanent colostomy in many patients. The operative techniques are such that the urologist must play a major role in planning and execution, thus improving the quality of life of many of these patients with double incontinence.

Indications and Contraindications for Conservative and Operative Therapy of the Neurogenic Bladder

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Systematised conservative treatment led to a marked decrease in urinary diversion. Among 75 children with neurogenic bladder (mostly spina bifida), 35 urodynamic studies have been collected.

Bladder outlet resistance increased in about half of the cases, between 5 and 6 years. From the 7th year of life, detrusor function may deteriorate together with a tendency towards decreasing bladder outlet resistance. After conservative treatment, improvement in urodynamic parameters can be documented.

Two of 75 children had unilateral nephrectomy, in 2 others supravesical diversion was performed. In principle, we favour keeping the bladder intact unless the findings suggest that this is unwise. If diversion is required, procedures using the bladder (Mitrofanoff, autoaugmentation, cystostomy) are preferred to intestinal diversions.

Longitudinal Management of Myelomeningocele with Preservation of Urinary Tract Integrity

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Most patients with myelomeningocele (MMC) are born with normal upper urinary tracts and the progressive damage that can occur is largely related to bladder dysfunction. Urological management of children with MMC has undergone steady refinement such that fewer patients develop renal failure. Lapides' introduction of clean intermittent catheterisation was the first big step in this direction. The next advance was McGuire's principle of the leak point pressure that permits identification of patients at risk of damage.

Using these principles for 8 years in more than 300 patients with MMC and its variants, we have reached a point where we can virtually guarantee preservation of upper tract integrity. With pressure-based management we have also found that vesicoureteric reflux rarely requires operative intervention, febrile urinary tract infections are uncommon, and long-term bladder compliance is preserved.

Fetal Development of the Human Urethral Sphincter

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A morphological study was carried out on 25 human embryos (3–60 mm crown-rump (CR)) and 20 human fetuses (15–40 weeks). The anatomical analysis was completed by immunocytochemical studies of different markers of muscle differentiation (vimentin, desmin, titin, and isoforms of the myosin heavy chain).

Mesenchymal condensation forms around the urethra after division of the cloaca (EH 12–15 mm CR). The puborectalis muscle appears in 22–30 mm CR embryos, following the opening of the anal membrane. Striated muscle fibres can be clearly differentiated at 15 weeks. At this time the smooth muscle layer also becomes thicker at the level of the bladder neck and forms the inner part of the urethral musculature. The urethral sphincter is a functional unit composed of central smooth muscle fibres and peripheral striated fibres. In the human fetus this musculature develops mainly in the anterior wall of the urethra.

Recurrent Urinary Tract Infections and Infravesical Obstruction Based on Müllerian and Wolffian Remnants in Boys with Normal External Genitalia

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Persistent Müllerian duct structures, cystic lesions of the Wolffian ducts and cysts of the male prostatic utricle are very rare, especially in boys with normal external genitalia. The incidence is higher in individuals with hypospadias, intersex disorders and cryptorchidism. The lesions can give rise to recurrent urinary tract infections (UTI) and symptoms of lower urinary tract obstruction. We report a series of 8 boys with cystic lesions arising from the colliculus seminalis. They all had normal external genitalia and presented with infravesical obstruction and recurrent UTI. The age at presentation was between 2 months and 9 years. In most cases the obstruction could not be visualised by micturition cystography, ultrasound or routine cystoscopy. In all cases the obstruction was detected by urodynamic investigation. Cystoscopy and retrograde filling of the opening in the verumontanum with radio-opaque dye showed a well defined space between bladder and rectum. In 6 cases the obstruction was treated by transurethral incision of the tip of the colliculus; in 2 cases open removal of the mass was necessary.

The pathogenesis and nomenclature of the lesions are not generally agreed and terms such as obstructive ejaculatory duct cyst, urogenital sinus cyst, Müllerian duct cyst and seminal vesicle cyst are used both correctly and incorrectly.

The fact that the structures often remain empty while producing obstruction during micturition makes detection difficult. Our relatively large series of these anomalies emphasises the importance of urodynamics when infravesical obstruction is suspected, even in the neonate.

Hypospadias Repair: Modified Mathieu (Flip-Flap) Repair for Hypospadias with Moderate Chordee

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The advantage of the classical Mathieu repair in hypospadias surgery is the good cosmetic result and the lack of long-term complications as seen in preputial flap repairs. Another advantage is the possibility of performing a reconstruction of the preputial skin. Many European parents like their boys to retain the prepuce, and it also gives good cosmetic coverage of the operated glans. The disadvantage is the restriction of urethral lengthening to approximately 15 mm and the impossibility of correcting chordee.

We modified the Matthieu repair into an operation with a vascularised skin flap with the possibility of doing a partial chordectomy and shortening of the dorsal tunica albuginea without doing a circumcision, so that reconstruction of the prepuce remains possible.

The first principle of the operation is to leave the subcutaneous vascularised dartos layer attached to the skin flap and to free this layer over a large area, giving enough room to the flap to pull it to the tip of the glans without tension on the vessels. This layer can be opened in the midline with enough exposure to remove chordee. With a stay suture lateral in the tunica albuginea, Buck's fascia is undermined all the way to the dorsal midline. The neurovascular bundle remains intact in Buck's fascia. One 3/0 Prolene suture in the dorsal midline is sufficient to straighten the penis. The operation is concluded in the same way as a normal flip-flap procedure with the urethral orifice in the tip of the glans. The preputial skin can be closed eventually in 2 layers. A 12 F silastic splint which passes a 4 F feeding tube as a catheter is left *in situ* for 5 days.

We performed this operation with excellent results in 20 patients with a mean age at operation of 12 months and a 1-year follow-up.

Correction of Posterior Hypospadias: A Personal Technique

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Posterior hypospadias correction in children has always represented a difficult technical problem. This is particularly true in the case of 1-stage surgery, which cannot be performed just occasionally by inexperienced surgeons. We therefore assume that 2-stage procedures can still hold a definite place in paediatric surgical urology.

A new method is presented, based on the technical principles of both Duplay's and Mathieu's operations.

If no chordee is present, the procedure can be performed in 1 stage; otherwise a preliminary step to release the chordee is required.

A Y-shaped skin flap, 12–13 mm wide in the proximal portion and bifurcating in the distal tract in a straight branch reaching the apex of the glans and a lateral one of the same length on the prepuce, is incised along pencil marks on the ventral aspect of the penis.

In the proximal part, hypospadias is corrected according to Duplay; the distal defect is repaired using the lateral branch of the Y transposed over the medial one and sutured to it according to Mathieu. This technique has the main advantage of bringing the meatus up to the apex of the glans, not as in Duplay's, and presents no particular difficulties, unlike other 1-stage operations.

In our experience, the functional and aesthetic results are excellent, similar to those offered by Mathieu's method; no stenosis was observed, and a reduced number of fistulas (15.3%) comprised the only complication, successfully and easily corrected after 6 months.

Distal Urethral Advancement and Glanuloplasty for Distal Hypospadias: Preliminary Results

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Many techniques are available for the correction of coronal and subcoronal hypospadias, but none is universally recommended. We have developed a specific technique, the distal urethral advancement glanuloplasty operation (DUAGO).

A Y-shaped incision of the glans beneath the meatus is completed by a diamond perimeatal incision and a subcoronal circumcision. The distal urethra is mobilised for 0.5 to 1.5 cm, split dorsally and slid forward to the apex of the glans. A glanuloplasty completes the procedure.

From June 1988 to October 1990 this technique has been used in 68 patients affected by distal hypospadias, even with mild chordee. Ages ranged from 17 months to 11 years (mean 3.2 years). A transurethral catheter was left *in situ* for 2.8 days post-operatively.

The functional and cosmetic results are good after 3 to 30 months of follow-up. Simple meatal dilatations were performed on an out-patient basis in 6 patients. Two fistulas were surgically repaired.

The DUAGO is an effective and successful technique for most cases of distal hypospadias, and also if mild chordee is present; it has a low complication rate and excellent results.

Long Loop Vas Orchiopexy

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The treatment of an abdominal testis remains a surgical challenge. Three different approaches may be used instead of standard orchiopexy: staged orchiopexy, microsurgical autotransplantation and division of the spermatic vessels. With the latter procedure, an adequate testicular blood supply is provided by the anastomotic network of the vas artery, provided a sufficiently long loop vas is present.

From January 1985 to December 1988 we performed a long loop vas orchiopexy in 7/104 cases of documented abdominal testis (211 cases of non-palpable testis). At follow-up (minimum 20 months, maximum 4 years), 5 testes (71%) were normotrophic and 2 (29%) were hypotrophic. One of the 2 hypotrophic testes appeared enlarged immediately post-operatively, possibly due to a good arterial supply and insufficient venous drainage.

An impalpable testis is an abdominal testis in 75% of cases, and in approximately 15% of these the spermatic vessels are not long enough to permit a standard orchiopexy. The surgical approach to the non-palpable testis should be directly "abdominal" after division of the external oblique fascia and conjoined tendon, avoiding manipulation of the inguinal structures. This approach permits preservation of the vascular anastomoses of the vas artery and safe division of the spermatic vessels. Moreover, it gives wide intra-operative exposure to the canalicular-abdominal anatomy, with no need for previous diagnostic laparoscopy.

The long loop vas orchiopexy is successful in 50 to 89% of cases. It has the advantage of being quicker than a microvascular autotransplantation and requires only one operation. It should be considered whenever favourable anatomy is encountered. An adverse anatomical situation, such as underdeveloped vascular pedicles or insufficient anastomoses, are believed to be the main causes of failure and consequent testicular ischaemia.

Unilateral Nephrectomy in Patients with Posterior Urethral Valves: A Clinicopathological Study

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Over a 9-year period we reviewed 31 patients with posterior urethral valves (PUV) in whom 31 nephrectomies were performed. The aim of the study was to determine the underlying histological features related to non-function and to establish clinical correlations. In 30 of the resected renal units vesicoureteric reflux was present pre-operatively. Twelve patients had been diagnosed antenatally, thus allowing the early institution of appropriate prophylactic and therapeutic measures. In 11 of the latter group there was no clinical evidence of urinary tract infection (UTI) prior to nephrectomy, which was performed between 6 and 15 months of age (mean 8). Nineteen patients presented acutely (11 with UTI, 4 with a mass and 4 with failure to thrive). Nephrectomy was performed between 6 months and 6 years of age in this group (mean 18 months). In a double-blind manner we have compared the histological features of the resected kidneys in both groups. Dysplasia was found to be a prominent histological feature when the kidney was removed early in the absence of preceding overt UTI. In cases where the kidney was subjected to infection prior to diagnosis, the predominant histological features were chronic pyelonephritic scarring and hydronephrosis, with dysplasia being noted much less frequently. It would appear that the antenatal diagnosis of PUV, allowing earlier intervention, may have saved renal function in those kidneys presenting acutely in the post-natal period.

The Effect of Phenylpropanolamine on Incontinence in Children with Neurogenic Bladders

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In children with myelodysplasia and a low level spinal cord lesion (low lumbar-sacral), detrusor hyperactivity and dyssynergic urethral function form the main pathophysiological basis for incontinence. In neurogenic bladder disturbance, pharmacological treatment has mainly been focused on the use of anticholinergics and alpha-adrenoceptor antagonists. In this study the effect of the alpha-adrenoceptor agonist phenylpropanolamine (PPA) on incontinence and lower urinary tract pathophysiology has been evaluated in 10 children with detrusor hyperactivity and low level spinal cord lesions.

PPA decreased detrusor hyperactivity and also increased urethral pressure in some patients, while the baseline intravesical pressure was unaffected. In a double-blind cross-over study in 10 patients, continence improved during active treatment but not enough to make the patients continent. Residual urine volumes did not increase. Placebo was without effect. Plasma level analysis with a gas chromatographic-mass spectrometric method showed that the patients with a high plasma level (381 ± 114 ng/ml) had a better response than those with a lower level (176 ± 38 ng/ml).

PPA improves continence among myelodysplastic children with detrusor hyperactivity but high plasma levels are needed for treatment to be effective.

Enterocystoplasty and Gastrocystoplasty: Experience of the Divisions of Paediatric Surgery in the Region of Emilia-Romagna

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Between 1986 and 1990 we performed bladder augmentation on 18 patients (9 males and 9 females, average age 10 years 9 months); 13 had myelomeningocele, 4 had sacral agenesis and 1 a neurogenic bladder of uncertain aetiology.

Following urodynamic observation of a hyper-reflexic, low capacity and low compliant bladder, the augmentation was performed in 14 patients with complications of the upper urinary tract, in 2 patients who required an undiversion and in 3 who simply needed treatment for incontinence. We operated in the following way: in 12 cases we performed a sigmoid patch cystoplasty, in 1 case we used a tubular-shaped sigmoid segment, 2 other patients were given a cup patch ileocystoplasty and 1 an ileal patch. In our 2 most recent cases we performed a gastrocystoplasty. The augmentation was accompanied by Young-Dees trigonal tubularisation in 5 patients, in 1 patient by a sling procedure and in 1 by a continent type Mitroffanoff diversion. In 3 cases the appendix was temporarily implanted into the bladder to facilitate intermittent catheterisation.

At follow-up the upper urinary tract showed good recovery in 14 cases, 1 patient continued to suffer from chronic renal failure, while in 3 cases complications arose (1 ureteric necrosis, 1 stenosis, 1 bladder stone). Complete continence was achieved in 15 patients; 2 have shown unsatisfactory results and 1 is still incontinent and requires an artificial sphincter.

In our experience bladder augmentation has proved to be a valid procedure in the treatment of incontinence and in the reconstruction of the urinary tract in patients with neurogenic bladder. Many question marks remain over the long-term outcome; gastrocystoplasty, however, seems to avoid the problem of mucus production.

Long-Term Results of the Goebbel-Stoeckel Operation in the Treatment of Neurogenic Bladder in Girls

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Intermittent catheterisation, pharmacotherapeutics and enterocystoplasty are not always able to achieve total continence in children with myelomeningocele. To treat uncontrollable incontinence in girls, the authors propose associating the Goebbel-Stoeckel procedure (GS) with self-catheterisation: the bladder neck is suspended with a large and strongly stretched aponeurotic band. The bladder has to be a low pressure reservoir.

Fifteen girls underwent the GS procedure with an age range of 5–20 years (median 13.7). Eleven patients underwent an enterocystoplasty at the same time, including 4 undiversions.

Eight patients required an associated procedure.

In 5 patients early in our experience, early reintervention was necessary to adjust the degree of stretch of the aponeurotic band; too weak (4 cases) or too strong (1).

In 8 patients, late reintervention was needed because of bladder deterioration; enterocystoplasty or detubularisation of a cystoplasty with a tubular-shaped sigmoid were performed. Results were reviewed after a median follow-up of 8 years.

Good results were recorded in 12 patients (80%) with total urinary continence, self-catheterisation every 4 to 6 h and a normal social life, including 1 case with a 20-year follow-up and a pregnancy.

There were 3 failures (20%), all girls who had undiversion with a tubular-shaped bowel.

In our experience, the GS procedure associated with intermittent catheterisation appears reliable when the bladder is a low pressure reservoir. This is usually achieved by enhancing the bladder.

Endoscopic Treatment of Reflux: An Experimental Study Comparing Teflon with Collagen

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Endoscopic correction of vesicoureteric reflux in children has been performed in several hundred cases with the use of Teflon or cross-linked bovine collagen. The main criticism of this simple procedure is the potential migration of Teflon particles and the local pathological reaction. An experimental study was performed in 18 rabbits where either Teflon or collagen was injected into the bladder submucosa. Pathological examination of the bladder, lymph nodes, liver, lungs and brain was performed several months after the experiment to study migration and the local reaction. There was no local granulomatous reaction with collagen, while a local granulomatous reaction was found in the site of injection of Teflon and in one regional lymph node. Colonisation of collagen by histiocytes increases with time. No distant granulomatous reaction was noted with both injections on histological examination. A mineralogical technique was applied after homogenisation of lungs and brain to investigate the distant migration problem. A few particles of Teflon were observed in the lungs but not in the brain. The pathological significance of these particles remains unclear. The collagen preparation seems to be an alternative to Teflon paste for endoscopic correction of reflux.

Surgery of the Intravesical Ureter in Persistent Vesicoureteric Reflux

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Nine cases of post-operative persistence of vesicoureteric reflux were treated by a surgical approach to the intravesical ureter instead of a new reimplantation. Cystoscopy was performed and the treatment of choice determined according to the anatomical findings, which included 2 patients with mucosal bridges keeping the ureteric neo-meatus wide open, both after a Cohen operation, 1 for primary reflux and the other for reflux associated with a posterior urethral valve. Endoscopic resection of the mucosal bridges solved the problem.

In 3 patients the persistence of reflux (1 bilateral) was caused by too short a submucosal tunnel. In these patients a surgical technique was used based on the formation of a rectangular mucosal flap based at the bladder neck. The ureter is exposed, its calibre reduced but it is not freed from its insertion. The first 2 cases were tailored. In the other patient, associated with a neuropathic bladder, the ureter was only plicated and a sigmoid patch used. Three patients had a bad backing to the ureter giving a short tunnel. In these cases, 1 of which was a duplex, double-barrelled reimplantation, the ureters were freed from their neo-insertion, isolated, and fixed in a new position.

The final patient had a partial dehiscence of a tailored ureter. Simple closure of the hole and covering of the suture line with bladder mucosa solved the problem.

Neurogenic Bladder Duplication, Vaginal Duplication, Vesicovaginal Fistula, Urinary Incontinence and Vesicoureteric Reflux. Case Report. Treatment and Results Five Years Later

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A 5-year-old female patient, born with myelomeningocele (operated on immediately after birth) presented with frequent urinary infections and permanent dribbling of urine from 3 meatuses.

Urological investigation, including urodynamics, showed complete bladder duplication, each bladder receiving a single homolateral ureter, and a double vagina. The 2 bladders were functioning differently, 1 with a hypertonic external sphincter and the other a hypotonic sphincter, the latter one showed vesicoureteric reflux and a fistula with 1 vagina.

A transureterostomy was performed, draining the refluxing ureter to the other one. This resolved the vesicoureteric reflux and stopped the flow of urine to the totally incontinent bladder and to the vagina. With clean intermittent catheterisation of the still functioning bladder, the urinary infections decreased in frequency and the patient became dry.

Five years later, renal and bladder conditions are stable.

RARE-MR Urography: A New Method to Visualise Urinary Tract Abnormalities in Children

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Magnetic resonance imaging (MR) with RARE (Rapid Acquisition with Relaxation Enhancement) mode depicts, selectively, fluid-containing compartments. This is achieved by predominant T_2-weighted sequences (23 s/slice). By adding conventional T_1-images the urinary tract is visualised with the surrounding parenchyma (7 min/image). From September 1989 to December 1990, 59 investigations were performed in 55 neonates, infants and schoolchildren who were found to have abnormal ultrasound findings. The RARE-MR was compared with intravenous and isotope urograms. Mild oral sedation was necessary in infants and toddlers.

Results showed that the quality of image was good in 56 of 59 investigations. The correct diagnosis, based on surgery or alternative techniques, is shown in the Table.

Correct diagnosis	*No. of studies (%)*	
Pelviureteric obstruction	19/19	(100)
Megaureter/dilated ureter	11/11	(100)
Dilated pelvis from reflux (> grade 2)	10/12	(83)
Dilated ureter from reflux (> grade 2)	9/12	(75)
Ureterocele	2/4	(50)
Renal duplications	8/8	(100)
Renal cysts	8/8	(100)

In conclusion, RARE-MR is a new technique that gives a reliable morphological image of the urinary tract independent of excretory renal function. This is an advantage over intravenous urography, particularly in neonates. Thus a combination of ultrasound, scintigraphy and RARE-MR urography can replace an intravenous urogram under some circumstances.

A Fetal Lamb Model of Partial Urethral Obstruction: Effects on the Developing Bladder

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The functional effects of outflow obstruction on the immature lower urinary tract have only recently come to be appreciated. The spectrum of post-obstructive bladder dysfunction in children is well recognised in such urological diseases as posterior urethral valves, prune belly syndrome and neurogenic bladder. The purpose of this study was to establish an animal model capable of reproducing partial urethral obstruction in the fetus in order to study its effects on the developing urinary tract and in particular the bladder.

Fetal lambs (at 90 days' gestation) underwent surgical placement of a constricting ring at the level of the bladder neck with concomitant ligation of the urachus (n = 12). Control animals underwent urachal ligation only (n = 6) After normal 150-day gestation, 10 surviving lambs in the partial obstruction group and 6 in the control group underwent a cystometrogram, evaluation of renal function and anatomical and histological evaluation of the lower urinary tract. The results showed myogenic failure of the bladder in a majority of the partially obstructed animals, marked detrusor hypertrophy as demonstrated by increased bladder weight and preservation of renal function.

By changing the timing of onset of the partial obstruction, the duration of the obstruction or by relieving the obstruction, we believe that this reproducible animal model can provide a better understanding of the physiological response of the developing urinary tract to infravesical, partial obstruction.

Electron Microscopic and Urodynamic Investigations of Neurogenic Bladders in Children

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During the last 6 years, biopsy specimens of 80 children with urinary tract anomalies were examined by electron microscopy. Samples taken at surgery were studied by a Jeon 100-B electron microscope. Urodynamic investigations were performed using Wolf apparatus. Ten children with a variety of types of neurogenic bladder and 10 with other urinary tract anomalies underwent both urodynamic investigation and also electron microscopic examination of their tissue in order to study the bladder smooth musculature. Changes were compared with normal controls.

The findings included fewer nerves scattered in the muscle, an increase in collagen fibres and destroyed muscle layer and hypertrophy of the muscle cells in infants and younger children. Other findings included serious deterioration in quality and quantity of the muscle cells in high resistance outflow bladders in older children and in large atonic bladders. The urodynamic findings correlated with the electron microscopic findings.

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Case Reports

Urethral Calculi Caused by Cholestyramine

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We report a case of spontaneous passage of urinary tract calculi caused by the treatment of hypercholesterolaemia with cholestyramine, which has not previously been implicated in the development of urinary tract calculi.

Case Report

A 56-year-old man attended the urology clinic complaining of the passage of calculi *per urethram*. This had occurred 2 weeks after he had started to take Questran (Bristol-Myers Pharmaceuticals) for hypercholesterolaemia. The patient stated that on 3 previous occasions he had taken cholestyramine and on each occasion he had started to pass small calculi *per urethram* 4 days after commencing treatment. The calculi would gradually become larger and he would stop taking cholestyramine, whereupon the passage of calculi ceased. There were no associated urinary symptoms. Examination was unremarkable.

Haematological investigations, including urea and electrolytes, liver function tests, proteins, calcium, phosphate and urate, were all normal on more than one occasion. The stones, which appeared to be of uric acid composition to the naked eye (Fig.), were composed of calcium, oxalate, uric acid and phosphate. A mid-stream specimen of urine was sterile but contained uric acid crystals. Three 24-h urine collections contained normal levels of calcium, creatinine and uric acid with a pH varying from 4.9 to 5.0. A cystine screen was negative. Intravenous urography was normal apart from calcification in the prostate gland.

The patient was reviewed 1 month later. At this time he reported the passage of a few smaller stones immediately after his first visit but none recently and he had now stopped taking cholestyramine. One year later he reported that on one occasion he had passed a few tiny calculi *per urethram*, but this was unrelated to cholestyramine usage.

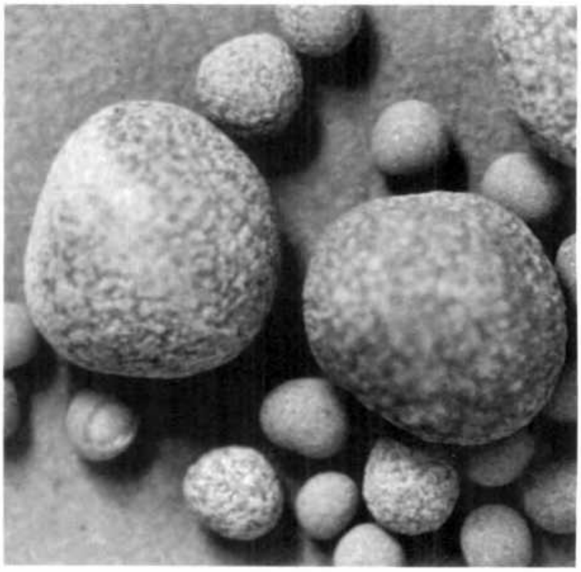

Fig. Smaller stones passed initially, larger stones passed later.

Comment

Cholestyramine causes metabolic acidosis (Eaves and Korman, 1984). We postulate that the acidification of the urine brought about by cholestyramine precipitated the development of uric acid calculi perhaps around small calcific concretions present in the prostate gland. This could be due to the cation exchange effect of the drug. Cholestyramine decreases urinary oxalate in the presence of hyperoxaluria but not when urinary oxalate is normal (Caspary, 1977; Caspary *et al.*, 1977).

The temporal relationship between the commencement of cholestyramine and the development of urethral calculi, together with their increasing size when treatment continued and disappearance when treatment stopped, support cholestyramine as the causative agent. As far as we are aware, this is the first recorded case of urinary tract calculi caused by cholestyramine.

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Spontaneous Perforation of an Augmented Bladder

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Case Report

A 38-year-old woman presented with a 1-day history of difficulty passing urine and a 1-week history of frequency, dysuria and suprapubic pain. Five years previously, at another institution, she had undergone bladder augmentation for detrusor instability using a detubularised segment of ileum. On examination her temperature was 37.8°C and suprapubic tenderness and guarding were elicited. Catheterisation revealed a residual volume of 1000 ml of urine which grew *Escherichia coli* on culture. She was given antibiotics and although she became apyrexial overnight, she continued to complain of lower abdominal pain. An intravenous urogram was normal and an abdominal ultrasound scan revealed free intraperitoneal fluid. A sample was aspirated and the creatinine value was 1180 μmol/l. A cystogram showed extravasation of contrast material from the right side of the bladder (Fig.). At laparotomy, a perforation was present at the ileo-detrusor anastomosis where the bladder had become adherent to the abdominal surface of the previous midline incision. The bladder was partially full and the indwelling Foley catheter was covered with a mucus plug. The catheter was changed and the bladder perforation was closed in 2 layers. The patient made an uncomplicated recovery and had a normal cystogram prior to discharge.

Comment

Spontaneous perforation is a rare complication of bladder augmentation and has been reported in 16 patients (Rao *et al.*, 1977; Elder *et al.*, 1988; Rink *et al.*, 1988; Rushton *et al.*, 1988; Sheiner and Kaplan, 1988). The following aetiological factors have been suggested: (a) trauma secondary to intermittent self-catheterisation, (b) urinary retention secondary to mucus plugs or poor compliance and (c) tearing of adhesions between the augmented bladder and the abdominal wall. We feel that the cause of the perforation in our patient was the tearing of adhesions between the augmented bladder and the anterior abdominal wall secondary to acute retention caused by a mucus plug. Fifteen of the previously reported patients had been performing intermittent self-catheterisation and 2 have had further perforations. Although the majority of perforations occurred at a site other than the augmentation anastomotic line, the type of bowel used seems to be of little consequence as perforations have been reported with all types of bowel augmentations. Perforations have occurred as early as 5 weeks and as late as 12 years after augmentation (Rao *et al.*, 1977; Sheiner and Kaplan, 1988). The cystogram showed a leak in only 50% of previously reported cases. If the condition is suspected, the patient should have an abdominal ultrasound examination and, if present, intraperitoneal fluid should be aspirated for biochemical estimation. Although it has been reported that early diagnosis may allow conservative management with catheter drainage and intravenous antibiotics, a delay in diagnosis may be fatal (Rink *et al.*, 1988). If patients are clinically unstable and a perforation is suspected, a laparotomy should be performed.

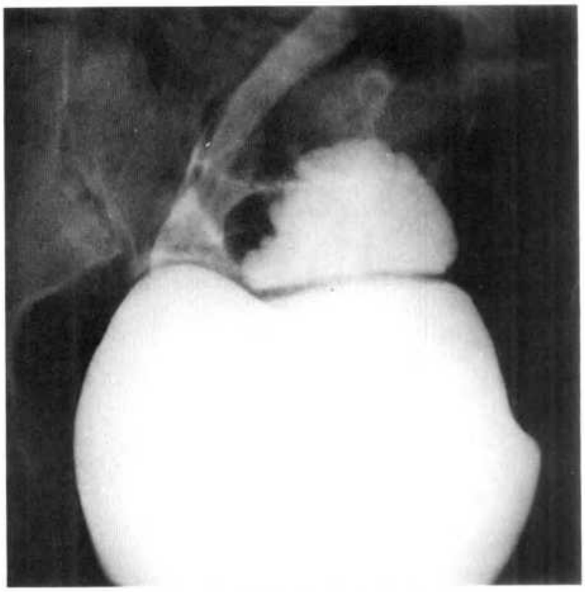

Fig. Cystogram showing extravasation of contrast.

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Congenital Ureteric Valves

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Case Report

A 21-year-old man was admitted acutely with left loin pain and no lower urinary tract symptoms. Physical examination and routine blood and urine tests were normal. A plain abdominal X-ray revealed no evidence of a stone, but an IVU showed that the left collecting system was dilated. Delayed films failed to show the site of obstruction. The right kidney and ureter were normal. Retrograde ureterograms subsequently confirmed the obstruction 1 cm below the pelviureteric junction and delineated a cusp-like valve at this site (Fig.). The rest of the ureter was normal. Following decompression, a ^{99m}Tc DMSA renogram showed the left kidney to have normal function, and a disconnected pyeloplasty was performed through a loin incision. The affected segment was excised and a cusp-like valve was seen within. Unfortunately, due to incorrect sectioning, the lesion could not be identified histologically.

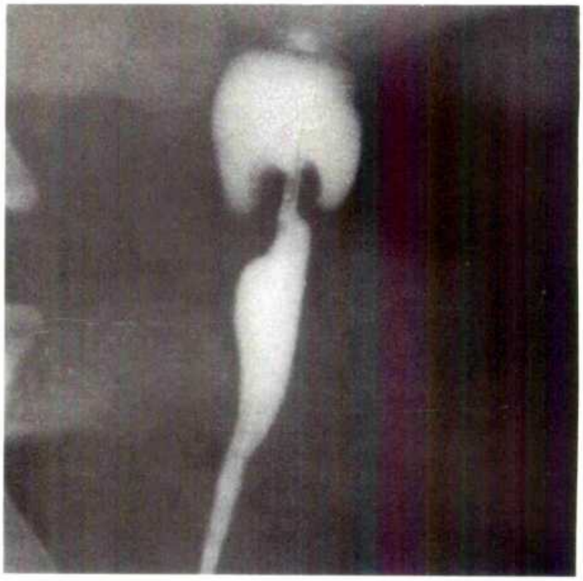

Fig. Retrograde ureterogram outlining a cusp-like ureteric valve.

Comment

Ureteric valves are an uncommon cause of ureteric obstruction. To distinguish true ureteric valves from non-obstructive folds, Wall and Wachter (1952) put forward 3 criteria: (1) anatomically demonstrable transverse folds of ureteric mucosa which contain bands of smooth muscle; (2) changes of obstructive uropathy above the valve, with a normal urinary tract below; (3) no other evidence of mechanical or functional obstruction. Criteria 2 and 3 were satisfied in the present case, but not the first. Although the valve was identified at operation, transverse histological sections failed to reveal it. Reinberg *et al.* (1987) pointed out that valves may easily be missed unless longitudinal sections are specifically requested. They also argued that it is possible to have an obstructing ureteric membrane which is devoid of smooth muscle.

Many patients have been successfully treated at open operation by excision and reconstruction, but percutaneous and endoscopic ablative techniques now seem to offer a viable alternative. Ureteric valves are difficult to diagnose prior to operation but must be kept in mind, since the diagnosis and treatment may be performed using minimally invasive endoscopic techniques at the same procedure. Resection specimens should always be sectioned longitudinally, with prior consultation with the pathologist.

Acknowledgements

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Kidney Rupture and Psoas Abscess after ESWL

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Case Report

A 69-year-old woman with a 9-month history of left loin pain, intermittent haematuria and a left staghorn calculus was referred for extracorporeal shock wave lithotripsy (ESWL). Following insertion of a ureteric double-pigtail stent (Sof-flex Multilength, Cook Urological), ESWL (3000 shocks/20 kV, Dornier HM3 lithotriptor) was administered. Post-treatment radiographs showed partial stone fragmentation (Fig. 1) and the patient underwent a second ESWL treatment (3000 shocks/20 kV) 5 weeks later.

Subsequent radiographs showed persistence of the pelviureteric junction (PUJ) calculus with widespread scattered calcific densities throughout the left upper quadrant. The patient was asymptomatic and the double-pigtail stent was removed, but because of the unusual radiographic appearance a CT scan was performed and this confirmed calcific fragments in renal and peri-renal tissues and swelling of the left psoas muscle (Fig. 2A).

Four months later the patient noted discomfort and swelling in the left iliac fossa. Examination confirmed low grade pyrexia and a tender indurated swelling above the left inguinal ligament. Repeat CT scan showed appearances of a psoas abscess (Fig. 2B). Isotope renography confirmed non-function in the left kidney (which prior to commencement of ESWL had shown normal excretion on IVU). Left nephrectomy and drainage of the abscess were performed and the patient made an uneventful recovery.

Sections through the resected kidney showed complete loss of the renal pelvis with multiple abscesses at the corticomedullary junction. Histology showed widespread destruction of renal parenchyma with fibrous tissue replacement, intense chronic inflammatory and foreign body giant cell infiltrate and numerous calcified bodies scattered throughout. Standard and mycobacterial microscopy and culture of the pus were negative.

Comment

Morphological renal changes occur in over half of the patients who are investigated after ESWL treatment (Ackaert and Schröder, 1989) but major disruption to a kidney has not been documented. The risk of distal ureteric obstruction is an indication for prior insertion of a ureteric stent (Atala and Steinbock, 1989) to allow adequate

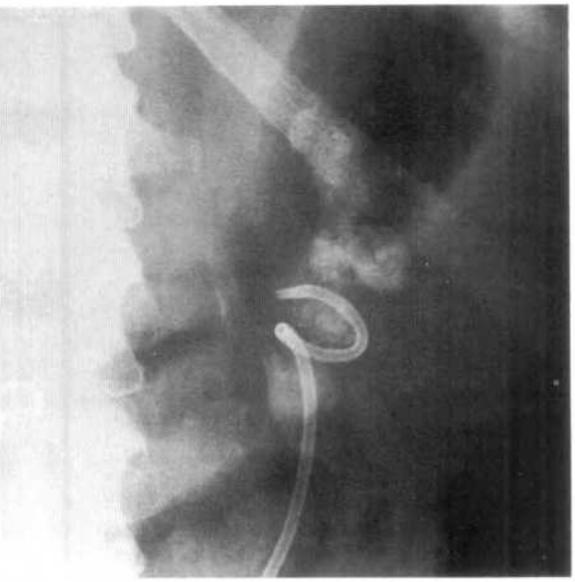

Fig. 1 Appearances of left renal calculi with persistence of PUJ calculus and partial fragmentation of the pelvicaliceal calculus following the first ESWL treatment.

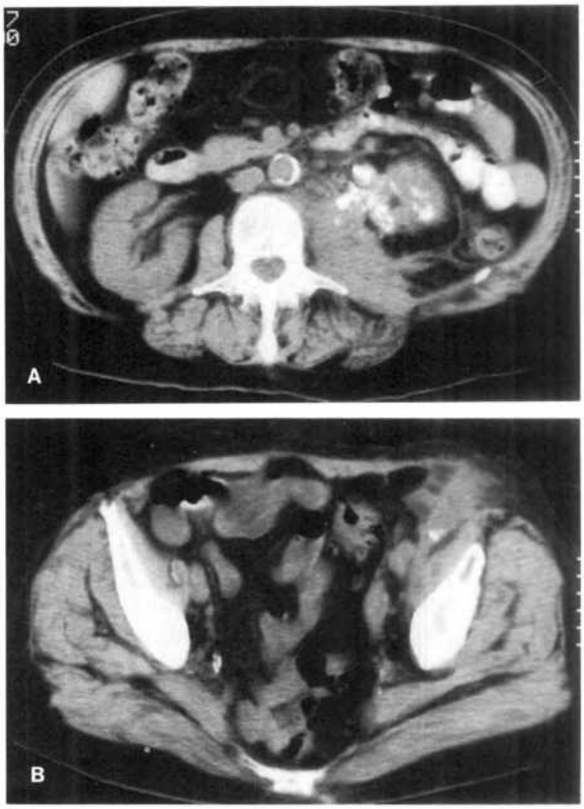

Fig. 2 CT scan (A) at the level of the kidneys showing left peri-renal oedema, calcific debris and swelling of adjacent psoas, and (B) more caudally, showing inflammatory changes extending to the left lower psoas and anterior abdominal wall.

drainage and preservation of function during ESWL. In our patient, however, stenting proved insufficient to protect the kidney and a virtual "explosion" of the calculus occurred with dissemination of calcific debris, extravasation and inflammatory necrosis extending to surrounding tissues, necessitating ultimate removal of the kidney.

Guidelines to define optimal treatment for staghorn calculi by combining ESWL, percutaneous nephrolithotripsy or open surgery, have been suggested (Di Silverio *et al.*, 1990) and, with hindsight, surgical management in our patient might have avoided the major sequelae described. This case emphasises that careful selection of patients remains paramount when electing to manage large renal calculi by ESWL.

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Requests for reprints to: T. Davidson, Department of Surgery, Westminster Hospital, London SW1P 2AP.

Oxybutynin and Incontinence during Grand Mal Seizures

D. HARARI and J. G. MALONE-LEE, *Urodynamics Department, St Pancras Hospital, London*

Case Report

A 30-year-old man with long-standing idiopathic epilepsy was referred because he was invariably incontinent during generalised epileptic seizures. These occurred frequently despite considerable therapeutic efforts. He was also occasionally incontinent at night, probably as a result of fits. Oxybutynin was commenced at a dose of 5 mg twice daily, on the assumption that the incontinence experienced during a seizure was due to hyper-reflexic detrusor contractions which may have been poorly coordinated and therefore likely to be compromised by an anticholinergic drug. The patient returned after 3 weeks on treatment and reported complete resolution of his incontinence despite having had 3 fits during this period. On review 2 months later, he was still continent despite continuation of his seizures.

Comment

Oxybutynin chloride exerts an anticholinergic effect on the detrusor muscle and also has a direct effect on the muscle due to inhibition of calcium-release and calcium-influx (Anderson and Fredericks, 1977). The drug has been shown to have statistically significant benefits over placebo in the treatment of urinary incontinence due to idiopathic detrusor instability (Riva and Casolati, 1984) and detrusor hyper-reflexia (Koyanagi *et al.*, 1986). This is the first reported case showing its effectiveness in controlling incontinence during generalised seizures. In patients suffering from poorly controlled epilepsy the incontinence is a particularly inconvenient complication of the seizures; oxybutynin may be of use in such circumstances.

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Requests for reprints to: J. G. Malone-Lee, Department of Geriatric Medicine, St Pancras Hospital, St Pancras Way, London NW1 0PE.

Metastatic Carcinoma of the Kidney Presenting to the Oral Surgeon

R. PERSAD, G. JONES and J. C. GINGELL, *Departments of Urology and Oral Surgery, Southmead Hospital, Bristol*

Case Report

A 62-year-old woman was referred by her dentist with an enlarging 2.5 × 2 cm reddish lesion in the right side of her mouth which was firm but pulsatile on examination. A haemangioma was suspected and "confirmed" on arteriography (Fig.). As the feeding vessels of the lesion were tortuous, embolisation was contraindicated and surgery performed instead. A lengthy operation was undertaken at which the external carotid artery was ligated, the lip split and the "haemangioma" dissected off the oral soft tissues and mandible. Histological examination later

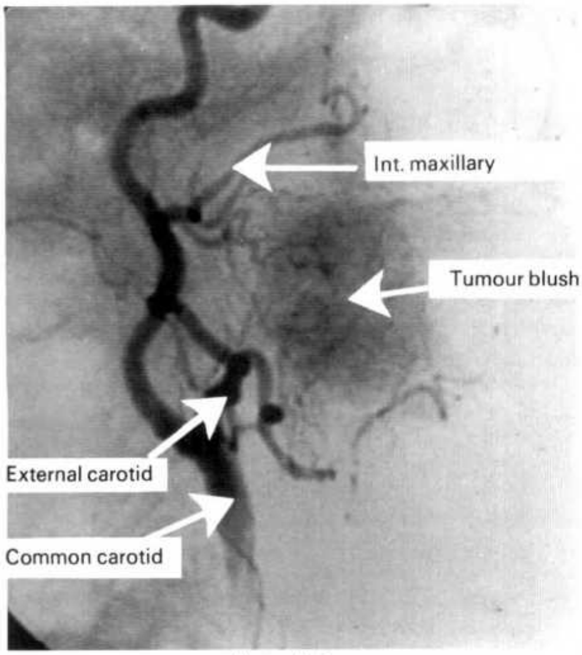

Fig. Arteriogram showing tumour blush.

showed the lesion to be a highly vascular secondary tumour of renal origin. Subsequent abdominal CT scan showed a 5-cm renal carcinoma in the upper pole of the right kidney. Post-operatively the patient developed severe pain in her right thigh and X-rays revealed a solitary metastasis in her femur. This was pinned and irradiated. Nephrectomy was not carried out because of the presence of metastatic disease.

Comment

More than half of the patients who present with jaw metastases have symptoms of their metastasis before the primary lesion is discovered. In the diagnosis of a destructive lesion of the mandible or maxilla, metastatic malignancy must be considered. The commonest sites of the primary are breast (33%), lung (18%), kidney (16%), thyroid (6%), prostate (6%) and colon (6%) (Clausen and Paulsen, 1963). Histochemistry can help to identify the primary tumour. Metastatic spread to the jaw from the kidney is probably haematogenous (Van der Kwast and Van der Waal, 1974), as bone marrow does not contain lymphatics. Metastatic spread is probably via Batson's "valveless vertebral venous" plexus, which provides little resistance to the upward propagation of tumour emboli.

The decision on whether or not to undertake nephrectomy in the presence of metastases is a debatable one. Nephrectomy may be warranted if symptoms are severe or if the patient is undergoing and responding to immunotherapy (with interleukins or interferons), when a reduction in the tumour burden may improve the outcome (Otto *et al.*, 1987). It is also recognised that soft tissue metastases are more likely to respond to immunotherapy than are bony ones.

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Requests for reprints to: R. Persad, Department of Urology, Bristol Royal Infirmary, Bristol BS2 8HW.

Leiomyosarcoma of Kidney

V. S. THIRUMAVALAVAN, C. L. KENNEDY and H. K. AL-RUFAIE, *Departments of Urology and Pathology, West Suffolk Hospital, Bury St Edmunds*

Case Report

A 69-year-old woman was admitted with flank pain, haematuria and weight loss. Examination revealed a tender mass confirmed on ultrasound to be a left renal tumour, and a radical nephrectomy was performed. On cut section the kidney was replaced by a necrotic, haemorrhagic tumour measuring 12 × 10 cm which had infiltrated the capsule. Microscopy demonstrated a predominantly spindle cell malignant tumour, the cells of which were arranged into fascicles and had numerous well orientated myofibrils, clearly demonstrated by PTACH and haematoxylin and eosin and Masson's trichrome stains (Fig.). Immunohistochemistry confirmed a leiomyosarcoma.

Comment

Up to 3% of renal tumours are sarcomas and a review of the literature reveals only 90 cases of leiomyosarcoma. Malignant leiomyoma was first reported by Berry in 1919. The patients ranged in age from 3 to 86 years, the majority being between 40 and 70. The tumour occurs equally on both sides.

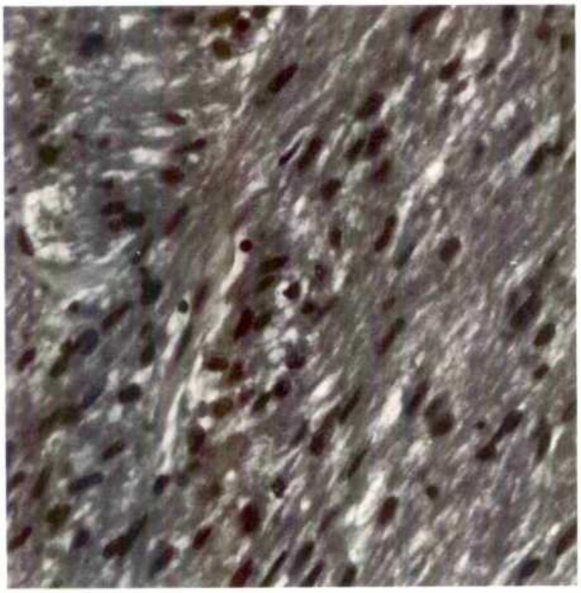

Fig. Leiomyosarcoma in left kidney. (H and E × 50).

Patients usually present with flank pain, haematuria and an abdominal mass. Weight loss and gastrointestinal symptoms also occur. The clinical, pyelographic and angiographic appearances are not characteristic. Surgery is the only potentially curative treatment. Both pre- and post-operative radiotherapy and chemotherapy have been tried but have failed to show lasting benefit. Despite radical nephrectomy, the tumours run an aggressive clinical course and early local and distant recurrence is common. Favourable histological criteria include lack of invasion into surrounding structures, but few mitoses do not necessarily equate with a good prognosis (Rakowsky *et al.*, 1987). Immunostaining for growth fraction with antibody Ki-67 has shown a good correlation with subsequent tumour behaviour (Krech *et al.*, 1989). Most patients succumb within a year of diagnosis, but isolated cases of long-term survival for up to 12 years have been noted.

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Requests for reprints to: V. S. Thirumavalavan, Department of Urology, West Suffolk Hospital, Bury St Edmunds IP33 1QZ.

Bilateral Synchronous Seminoma

J. R. WILLIAMS, M. A. STOTT and C. U. MOISEY,
Department of Urology, Royal United Hospital, Bath

Case Report

A 36-year-old man presented with a 2-month history of a painful swollen left testis. A right orchiopexy had been performed at the age of 12. On examination the left testis was hard and enlarged; the right testis was small and high in the scrotum. Ultrasound examination of the left testis showed a solid heterogeneous tumour. However, a well defined right intratesticular mass suggested a second tumour. Bilateral radical orchiectomies were carried out (Fig.). The patient's pre-operative beta-human chorionic gonadotrophin levels were elevated at 7 iu/l (normal <2 iu/l), with a level of 76 iu/l in the blood from the left cord. Serum levels fell to normal by the second post-operative day; alpha-fetoprotein levels were normal throughout. Histology showed bilateral seminomas with spread to the cord on the right side. A CT scan was normal.

Comment

Second testicular tumours are found in 2.6% of primary testicular tumour patients and the majority are metachronous. Synchronous tumours are very rarely found (Patel *et al.*, 1990). The contralateral testis should be screened immediately the diagnosis is made, especially in patients with known risk factors such as undescended testes, as in this case (Hoekstra *et al.*, 1983). Screening should be by

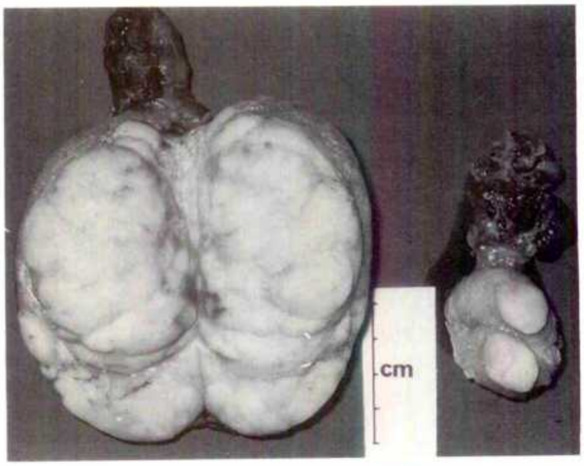

Fig. Both testes bisected to show the bilateral tumours with a deposit in the right cord.

ultrasound and self-examination and should continue indefinitely (Scheiber *et al.*, 1987).

Although rare, the clinician should look for synchronous tumours. Metachronous tumours are becoming more common with modern treatment, increasing the longevity of the patients with primary tumours (Patel *et al.*, 1990).

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Requests for reprints to: J. R Williams, Nuffield Department of Orthopaedics, Level 1, John Radcliffe Hospital, Headington, Oxford OX3 9DU

British Journal of Urology (1991), 68, 662

Points of Technique

Raising the Cervix by Finger for Closure of Vesicovaginal Fistulae

W. N. FAN and S. Z. ZOU, *Departments of Gynaecology and Urology, Nanchong Prefectural Hospital, Nanchong, Sichuan, China*

For 13 years we have used the transvesical approach to repair vesicovaginal fistulae in patients with a highly placed fistula, with a very small vagina or with a combined vesicovaginal and ureterovaginal fistula. The patient is placed in the lithotomy position and the abdomen, perineum and vagina are sterilised and draped as usual. The operator stands by the patient's left side. The bladder is opened and the fistula revealed. The operator's left index and middle fingers are inserted into the patient's vagina, elevating the cervix uteri and the fistula upward and forwards. By this procedure the fistula becomes higher and more superficial and is easier to close. If the fistula is near the opening of the ureter, a ureteric catheter must be inserted into the ureter to protect it from injury. An incision is made through the bladder mucosa around the fistula at the junction of the mucosa with the vagina; the vaginal mucosa is separated from the bladder for a distance of 1.5 to 2 cm on all sides; scar tissue is resected. Closure is effected in 3 layers using interrupted 3–0 chromic sutures. The vaginal mucosa is sutured longitudinally and the muscle and bladder mucosa transversely. A 14 F catheter is left in the bladder through the urethra for continuous drainage. The catheter is removed on the seventh to tenth day post-operatively and the patient discharged from hospital on the tenth or eleventh day.

Over the last 13 years we have treated 6 patients by this technique; their ages ranged from 22 to 39 years (average 30). All were closed at the first attempt and there were no complications.

Requests for reprints to: S. Z. Zou, Department of Urology, Nanchong Prefectural Hospital, Nanchong, Sichuan, China.

Catheterisation of the Tortuous Neo-urethra

K. A. R. HUTTON and D. F. M. THOMAS, *Department of Paediatric Surgery, St James's University Hospital and General Infirmary, Leeds*

Reconstructive operations for epispadias, severe hypospadias and congenital bladder neck incontinence (Young–Dees–Leadbetter procedure) can produce a tortuous urethra which is difficult to catheterise. In this situation there was previously little alternative to suprapubic diversion to establish bladder drainage following secondary urethral instrumentation or endoscopic surgery, *e.g.* cold knife urethrotomy. Since the tortuosity can invariably be negotiated under direct vision, the availability of a paediatric Foley catheter designed for introduction over a guide wire now makes it possible to catheterise the "difficult" neo-urethra.

Technique

If conventional catheterisation cannot be achieved, a suitably sized catheterising cysto-urethroscope is negotiated through the neo-urethra under direct vision. A 3 F flexible tipped guide wire (Cat. No. 105128082, Polystan, Nottingham) is advanced into the bladder via the catheterising channel. With the guide wire maintained in position, the endoscope is removed and the catheter (Cat. No 732010025 10F, Polystan, Nottingham) introduced over the guide wire. After inflation of the balloon the guide wire is withdrawn.

We have successfully employed this technique to catheterise the neo-urethra in cases of epispadias and following Young–Dees–Leadbetter reconstruction. The procedure is straightforward and considerably less likely to cause urethral trauma than blind attempts at catheter insertion. It avoids the need for suprapubic diversion in cases where urethral drainage is more appropriate.

Requests for reprints to: D. F. M. Thomas, Department of Paediatric Surgery, St James's University Hospital, Beckett Street, Leeds LS9 7TF.

British Journal of Urology (1991), **68**, 663–665

Correspondence

Dear Sir,

re **Blunt renal trauma in childhood. Features indicating severe injury.** D. M. Quinlan and J. P. Gearhart. *Br. J. Urol.*, **66,** 526–631, 1990.

The authors present a group of 50 paediatric patients with blunt renal trauma to evaluate the presence of clinical clues for major renal trauma. They conclude that the "number of associated injuries in this study was high" (34/50 patients). We think that this number is quite normal in this particular type of accident, especially when the relatively high number of pedestrians (26/50) is taken into consideration. In our study of 121 children we found associated injuries in 59 (48.8%) (J. D. M. de Vries *et al. World J. Urol.*, **7,** 218–222, 1990).

Unfortunately, the authors did not categorise their patients into clinically definable classifications, *e.g.* injury severity score (S. P. Baker *et al. J. Trauma*, **10,** 719–721, 1974), that showed a good correlation with the significance of the urinary tract trauma (S. J. M. Monstrey *et al. Br J. Urol.*, **60,** 393–398, 1987). Comparison with other studies is therefore difficult. We regret that the authors state that in "only" 10% there was a false positive incidence in gross haematuria and a false negative incidence of "only" 10% in the microscopic haematuria group. Since we are dealing with "only" 20% major renal lesions and only 20% renal lacerations in this study compared with 20% grade II and 4.5% grade III lesions in our study, we feel that 10% limits are in no way insignificant. We found, for example, an incidence of pre-existing renal anomalies (always to be considered in this group) in 10% (12/121).

With regard to the haematuria, we disagree with the simplified differentiation between gross and microscopic haematuria, since a study at our clinic demonstrated that there is a much higher relevance to this finding if the microscopic haematuria is divided between macroscopic, intermediate and microscopic (S. J. M. Monstrey *et al. Ned. Tijdschr. Geneeskd.*, **27,** 1284–1288, 1985; S. J. M. Monstrey *et al. Br. J. Urol.*, **60,** 393–398, 1987). By applying the guidelines of the above article we would have missed the right diagnosis in 3 children. On totally different premises we also conclude that in the paediatric age group a complete radiological assessment is necessary in case there has been significant blunt abdominal trauma independent of clinical features such as haematuria and shock.

Yours faithfully,

J. D. M. de Vries,
Department of Urology, University Hospital,
Nijmegen, The Netherlands

Dear Sir,

re **BAUS UROLINK**

In writing about the challenge of the 1990s, you very much echoed the aims of UROLINK when you stated, "It can no longer be acceptable to pour resources into procedures that have poor outcome or poor quality of life. It can no longer be acceptable to ignore the health problems of those who do not have access to even basic medical care." (G. D. Chisholm. *European Urology Today*, **1,** 1991).

UROLINK (Urological Overseas Links) aims are to promote and encourage the provision of appropriate urological expertise and education worldwide with special emphasis on the poorer and less privileged parts of the world. UROLINK was formed as a Working Party of the British Association of Urological Surgeons in January 1990 and has focused on 4 main areas:

(1) Establishing links with overseas departments by personal contact.
(2) Helping to provide appropriate urological equipment and journals.
(3) Facilitating professional visits by urologists to work alongside colleagues in developing countries.
(4) Encouraging appropriate urological training of overseas surgeons both in the UK and in their own countries.

Those who attended the UROLINK session during the Annual Meeting of BAUS in Glasgow recently heard fascinating accounts from 3 members of the challenges and achievements of 3 very different overseas visits. A newsletter was distributed in May and we plan to keep BAUS members informed of UROLINK's activities.

But UROLINK is you—the urologist who sees the need for a fairer distribution of resources and a wider availability of knowledge which we already have. We would encourage every department to develop links with an overseas department, if they do not already have one; a trainee from a developing country can form the foundation of a link which can be nurtured by correspondence and supporting visits.

If you would like further information, please write to me. We are interested in your views and suggestions.

Yours faithfully,

N. W. Harrison, MD, FRCS, Chairman, BAUS UROLINK, 32 Westbourne Villas, Hove, East Sussex BN3 4GF.

re **Gamma-seminoprotein—a new tumour marker in prostatic cancer?** U. Maier and R. Simak. *Br. J. Urol.*, **65**, 509–512, 1990.
Correspondence from K. H. Scheit. *Br. J. Urol.*, **68**, 331–332, 1991.

Reply from Dr Maier. Professor Scheit refers to reports which claim that prostate-specific antigen (PSA) and gamma-seminoprotein are one and the same protein. In contrast, our study revealed differences in the simultaneous evaluations of both markers.

The cut-off level for each marker is obviously critical for sensitivity and specificity, yet we found in follow-up studies of patients with a known clinical history a contrary factor in the values of PSA and gamma-seminoprotein. In patients with a clinically unremarkable history, 26% showed not only a higher level of PSA but also a constant but false increase without clinical correlation. Only half of these patients showed the same tendency with gamma-seminoprotein. In the other patients in this group the gamma-seminoprotein levels correlated well with their clinical course. In patients with progressive disease the correlation between clinical course and PSA levels was better than the correlation between clinical course and gamma-seminoprotein levels.

In 1989 Arai *et al.* (*Urol. Int.*, **44**, 135–140) presented data which supported our findings. They too reported partly differing results from both markers in patients with prostatic cancer of the same T stage.

The reports cited by Professor Scheit, which suggest that PSA and gamma-seminoprotein are the same, could be accepted for routine evaluations if the marker curves were parallel. Our data did not show such a correlation.

Our assay kits came from different companies. It has been proved by Hortin *et al.* (*J. Urol.*, **139**, 762–765, 1988) that the results obtained were not directly comparable, although there was a marked proportional bias between two assays for the same marker.

We thank Professor Scheit for his comments. His arguments, however, do not explain our findings in an important group of patients.

Dear Sir,

re **Carcinoma of the bronchus and metastases from an occult testicular tumour.** G. A. Newaishy and C. G. Kelly. *Br. J. Urol.*, **66**, 659–660, 1990.

The authors of this Case Report base their diagnosis of testis tumour on the elevated beta HCG. There is no histological confirmation of a testis primary. My interpretation of this case is that it is a cancer of the lung producing beta HCG. Evidence of ectopic production of beta HCG by lung cancer was provided by A. H. Tashjian *et al.* (*Proc. Natl. Acad. Sci.*, **70**, 1419–1422, 1973) and S. A. Metz *et al.* (*Am. J. Med.*, **65**, 325–333, 1978). There is also evidence that lung cancer of all cell types produces beta HCG (P. Bunn and E. C. Ridgeway. (1989). Paraneoplastic syndrome. In *Cancer, Principles and Practice of Oncology*, ed. Devita, V. T. *et al.* Third edition. P. 1899. Philadelphia: Lippincott). The incidence of this elevation in small cell cancer is 1 to 32%, epidermoid cancer 19%, adenocarcinoma 17% and large cell cancer 20%. Therefore this patient probably has a lung cancer rather than metastatic testicular cancer.

Yours faithfully,

M. R. Shetty
Department of Medical Oncology, Northwest Community Hospital, Arlington Heights, USA

Reply from Dr Newaishy. Dr Shetty is entitled to his interpretation, which is based on the lack of histological confirmation of testicular tumour and that evidence has been reported of ectopic production of beta HCG. Our patient is different from those reported by others. He had an undescended testis, multiple rounded shadows of equal sizes in all zones of both lungs and his beta HCG level was 5640 iu/l. The normal level of beta HCG at our hospital is <3 iu/l. The ratio of elevation therefore is 1880:1. The patient reported by Metz *et al.* (1978) had no histological confirmation of the single shadow which appeared soon after lobectomy, had two testes and the beta HCG level was 21 ng/ml. The normal level at their hospital was <1 ng/ml.

The ratio of elevated to normal was 21:1. The other report (Tashjian *et al.*, 1973) was of established HCG-producing clones. The serum beta HCG concentration was <3 ng/ml; normal <1.0 (ratio 3:1). After culture, the rates of beta HCG production from 3 clones varied from <40 to 100%. The report gives more information and needs to be studied by those interested. Chapter 55, page 1899 of De Vita collects much information from the literature but does not give levels of elevation or actual figures of units. More information has been published in studies specifically geared to hormone production by lung carcinomas (C. Gropp *et al. Cancer*, **46**, 347–354, 1980; M. Hansen *et al. Cancer*, **45**, 1432–1437, 1980). Many hormones were found in the urine, sera and plasma of 75 patients with small cell bronchogenic carcinoma. Of these patients only ACTH, ADH, calcitonin and gastrin were elevated to a significant level. None of the other hormones (including beta HCG) was found to be significantly elevated (Hansen *et al.*, 1980). A similar study of 110 or more patients reported values of beta HCG elevated to 40 ng/ml. Values exceeding 2 ng/ml were considered elevated. The ratio of the greatest to normal levels was therefore 20:1. I would expect, therefore, that our patient's beta HCG was not from his bronchogenic carcinoma.

Dear Sir,

re **Carcinoma of the prostate masquerading as rectal carcinoma.** M. C. Foster and P. H. O'Reilly. *Br. J. Urol.*, **66**, 193–195, 1990.

I have read the above article with interest because the issue of rectal invasion by prostatic carcinoma is seldom treated in the literature.

Certainty about the prostatic origin is sometimes difficult even after rectal and prostate biopsy, since tumours are frequently undifferentiated or poorly differentiated adenocarcinomas (Gillat and Gingell. *J. Urol.*, **141**, 511a, 1989). Therefore, specific immunohistological staining techniques for prostatic specific antigen (PSA) must be used (Shevchuk. *World J. Urol.*, **5**, 89–91, 1987). In Case 3 of the above article orchiectomy was performed before definitive demonstration of the prostatic origin of the tumour, although the therapeutic trial was sufficiently demonstrative.

We have noticed that transrectal sonography is more sensitive and economic than computed tomography to show involvement of the rectal wall by prostatic cancer (Farina *et al. Arch. Esp. Urol.*, **43**, 1990). However, since many patients have involvement of the rectosigmoid colon with an undamaged distal rectum (Rubesin *et al. Am. J. Radiol.*, **152**, 53–57, 1989), barium enema should be performed if clinical data suggest rectal invasion.

Since we do not know what types of prostate carcinoma invade the rectum or the mode of progression, communication of cases like these is important. The prostatic capsule, if it exists at all (Ayala *et al. Am. J. Surg. Pathol.*, **13**, 21–27, 1989), and Denonvilliers' fascia—a thin collagen and smooth muscle layer (Benoit *et al. Eur. Urol.*, **11**, 222–232, 1985)—seem weak barriers to cancer progression.

Yours faithfully,

L. A. Farina
Urology Service, Fundación Puigvert, Barcelona, Spain.

Dear Sir,

re **Introduction of a Foley catheter by puncture suprapubic cystostomy.** B. Elem. *Br. J. Urol.*, **66**, 555–556, 1990.

This method of performing suprapubic cystostomy has been used in our department regularly. Sometimes one does not know whether one has entered the bladder or not. We have modified the trocar by incorporating a side channel in it. Once the bladder has been entered, urine will flow out through the side channel and one may take out the trocar and introduce the catheter.

Yours faithfully,

R. P. Rajan
Public Health Centre, Madras, India

British Journal of Urology (1991), 68, 666–667

Notices

British Association of Urological Surgeons

President: R. E. Williams, MD, ChM, FRCS, FRCSE

Annual Meeting: Bournemouth. 21–26 June 1992

Abstracts of contributions to be considered as either papers, posters or videos by the Programme Sub-Committee of Council should be submitted on the special forms, which will be available from the BAUS Secretariat in October 1991. Completed forms, which should state clearly whether the submission is a paper, a poster or a video, must be returned to the Honorary Secretary by Friday, 10th January 1992.

Abstracts not on the special forms will NOT be considered.

All correspondence to: R. J. Morgan, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

BAUS Travelling Fellowship

The British Association of Urological Surgeons offers a Travelling Fellowship of £1000.00 for any article(s) of outstanding merit published each year (2 volumes) in the British Journal of Urology. Candidates for the prize must be Fellows of the Royal College of Surgeons in the British Isles, Canada, Australia or South Africa; they must be undergoing urological training or have obtained a consultant post not more than 10 years before the date of submission of the paper. In the case of multiple authorships the authors would have to decide which of them should receive the prize. The successful prizewinner must submit a programme of visits to urological centres outside Britain. This prize is not necessarily awarded annually.

Scholarships for Experimental and Clinical Research in Urology

The European Association of Urology and the European Board of Urology will award three scholarships for research in Urology. Each scholarship will be awarded for one year, starting on 1 July 1992, at a maximum of 33,000 ECU at any appropriate institution in the world. Further information from: The European Board of Urology Education Committee, P.O. Box 25285, 3001 HG Rotterdam, The Netherlands. Tel: 31.10.436.6665. FAX: 31.10.436.6669.

Bard Award

This award, made possible by the generosity of C. R. Bard International Limited, was made for the first time at the Annual Meeting in Bristol in 1979. The award will consist of the sum of £1500 and the Bard Silver Medal. The award will be given for the best essay submitted specifically for consideration for the award by members of the Association (non-members must be sponsored by a Full Member).

Essays should be based on original work on any topic connected with urological surgery, either clinical or experimental. The essay should include a review of the literature and the clinical implications of the work performed. A panel of three adjudicators will be nominated at the February meeting of Council each year. Submissions for the award should be made in triplicate by 1 March to the Honorary Secretary. The winning essay will be read during the Annual Meeting and should not exceed 20 minutes in duration.

British Journal of Urology Travelling Fellowship

This fellowship of £1500 enables a Senior Registrar or numbered Career/Research Registrar to attend the Annual Meeting of the American Urological Association. It is awarded in April each year at the Annual Scientific Meeting of the Senior Urological Registrars Group (SURG). The award is given for the best paper presented at this meeting on a vote by the members of SURG present at the meeting. Invitations to the meeting are sent out in January by the Chairman of the Senior Urological Registrars Group and papers must be new work not previously published and not resulting from a thesis. An additional Fellowship may be awarded at the discretion of the British Journal of Urology and the Senior Urological Registrars Group.

Lewis Medical Travelling Scholarship

The scholarship covers travel, accommodation and registration expenses associated with attending the Annual Meeting of the American Urological Association. The scholarship will be available to any person appointed to a numbered urological training post and will be awarded to the person presenting the winning paper at the Annual Meeting of the Senior Urological Registrars Group. An additional scholarship may be awarded at the discretion of the Senior Urological Registrars Group and Lewis Medical Limited.

William Cook Travelling Fellowship

In 1990, William Cook Europe Limited generously offered an annual sum of £3000 to finance a minimum of three travelling fellowships each year. Candidates must be members of the British Association of Urological Surgeons. Applications should be made to the Honorary Secretary of BAUS by 1 February, giving the following information: the name of the centre to be visited, the reason for the visit and an estimate of the cost of travel and accommodation. Prior agreement to the visit must be obtained from the surgeon/hospital in question.

Applications will be considered by a BAUS Committee. Successful applicants will be required to submit a report on the experience gained in the centre visited.

Simpla Research Prize

The Simpla Research Prize was inaugurated in 1988 and consists of an annual prize of £1000 to support a clinical research project. Applicants should submit an abstract of not more than 500 words detailing the way in which, if successful, they would use the prize. These submissions should be made to the Honorary Secretary by 1 April. The prize will be awarded at the Annual Meeting of the Association.

Prizes and Awards

British Association of Urological Surgeons
President: R. E. Williams, MD, ChM, FRCS, FRCSE

At the 47th Annual Meeting of BAUS held in the Scottish Exhibition and Conference Centre, Glasgow on 25–28 June 1991, the following awards were made:

St Peter's Medal

At the Annual Dinner the President presented the St Peter's Medal to Mr J. L. Williams, after a citation given by Mr J. H. Steyn.

St Paul's Medal

At the Annual Dinner the President presented the St Paul's Medal to Dr Frank Hinman, Jr, after a citation given by Mr R. T. Turner-Warwick.

BAUS Travelling Fellowship

The 1991 prize was awarded to Mr S. C. W. Harrison for his contributions to Volumes 65 and 66, 1990.

DANTEC Urology Prize

The award for 1990 was given to Margaret Godley, P. G. Ransley and Helen Parkhouse for the paper entitled "Quantitation of vesicoureteral reflux by radionuclide cystography and urodynamics." *Pediatric Nephrology*, **4**, 485–490, 1990.

Surgitek Prize

The 1991 Surgitek Prize was awarded to Mr N. Clark for his paper entitled "Disodium pamidronate identifies differential osteoclastic bone resorption in metastatic prostate cancer."

Simpla Research Prize

The 1991 Prize was awarded to Mr P. M. Cuckow for his project entitled "A project to explore the role of Villin as a marker of renal adenocarcinoma."

Bard Award

The prize and Bard Silver Medal for 1991 were given to Mr S. N. Lloyd, Glasgow, for his essay entitled "Local hyperthermia for prostatic disease: *in vitro* studies on human prostatic cancer cell lines."

William Cook Travelling Fellowships

Fellowships were awarded to Messrs M. D. Dinneen, N. W. Harrison (on behalf of UROLINK) and B. Jenkins.

Lewis Medical Travelling Scholarship

The scholarship was awarded to Mr I. K. Dickinson.

British Journal of Urology Travelling Fellowship

The fellowship was awarded to Mr T. W. Carr.

British Journal of Urology (1991), **68**, 668–669

Diary

1992

January 10	Final date for submission of abstracts for the 1992 BAUS Annual Meeting.
March 8–13	19th Biennial Congress of the Urological Association of South Africa, Sun City, South Africa. Contact: Dr I. Lissoos, 1 Esselen Towers, Esselen Street, Hillbrow, 2001, South Africa.
March 19–21	Eleventh International Symposium of Operative Andrology. Istanbul, Turkey. Contact: Dr A. Kelâmi, Brahmsstrasse 32, D-1000 Berlin 45, Germany.
March 19–21	Searching for Prostatic Carcinoma: the Problem of Screening and Early Detection. Munich, Germany. Contact: D. Née, Secretariat, Department of Urology Krankenhaus der Barmherzigen Brüder, Romanstr. 93, W-8000 Munich 19, Germany. Tel: 89/1793-252 or 89/17 56 61. FAX: 89/1782653.
March 26–27	Eighth Annual Symposium on Progress in Paediatric Surgery, Oviedo, Spain. Contact: Dr J. L. Teixidor de Otto, Servicio de Cirugía Pediátrica, Hospital Central de Asturias, Centro Universitario, E-33006 Oviedo, Spain.
April 3–5	Third International Conference on Geriatric Nephrology and Urology. Toronto, Canada. Contact: Dr D. G. Oreopoulos, Peritoneal Dialysis Unit, Toronto Western Hospital, 399 Bathurst Street, Toronto, Ontario, Canada M5T 2S8. Tel: 416 364 9974. FAX: 416 360 8127.
April 9–11	6th International Urological Symposium. Girne, North Cyprus. Contact: Dr A. Kelâmi, Brahmsstrasse 32, D-1000 Berlin 45, Germany.
April 24–25	Annual Meeting of the Irish Society of Urology. University of Limerick. Contact: Honorary Secretary, Irish Society of Urology, at the Royal College of Surgeons in Ireland, 123 Saint Stephen's Green, Dublin 2, Ireland.
May 6–8	8th International Symposium on Radionuclides in Nephrourology, The Grosvenor Hotel, Chester, England. Contact: Mr P H O'Reilly, Department of Urology, Stepping Hill Hospital, Stockport, SK2 7JE.
May 10–14	American Urological Association, Washington Convention Centre, Grand Hyatt, Washington DC.
May 23–24	Société Belge d'Urologie: 57th Congress. Liège, Belgium. Contact: Dr F. F. Wart, 4 Avenue du Bois des Sartis, B-6111 Landelies, Belgium.
May 24–28	Inaugural Meeting of Pan African Urological Surgeons' Association, Harare, Zimbabwe. Contact: Mr A. P. Danso, Department of Surgery, University of Zimbabwe Medical School, P.O. Box A 178, Avondale, Harare, Zimbabwe.
June 4–6	Fourth International Meeting of Andrology, Como, Italy. "Treating Male Infertility: New Possibilities". Contact: Dr G. M. Colpi, II Divisione di Chirurgia, Centro di Andrologia e Infertilita, Ospedale "VALDUCE", Via Dante 11, I-22100 Como, Italy.

June 10–12	Continent Urinary Reconstruction. First International Meeting. Lund, Sweden. Contact: Dr Wiking Månsson, Department of Urology, University Hospital, S-22185 Lund, Sweden.
June 22–25	Canadian Urological Association Annual Meeting, Winnipeg. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.
July 22–25	European Association of Urology, 10th Congress, Genoa. Contact: Conference Secretariat, Top Congress—P.R., Piazza Galeazzo Alessi 2/1, 16128 Genoa, Italy.
June 23–26	BAUS Annual Meeting, Bournemouth International Centre, Bournemouth. Contact: BAUS Office.
August 24–27	Third European Symposium on Uroradiology. Herlev, Denmark. Contact Dr H. S. Thomsen, Department of Diagnostic Radiology 54E2, Herlev Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark.
August 24–27	VIIth International Symposium on Urolithiasis and Related Clinical Research. Cairns, Australia. Contact: Dr Rosemary L. Ryall, Department of Surgery, Flinders Medical Centre, Bedford Park, South Australia 5042.
September 3–6	Tenth World Congress on Endourology and ESWL, Singapore. Contact: Secretariat, c/o Department of Urology, Singapore General Hospital, Outram Road, Singapore 0511.
September 14–18	Fifth World Meeting on Impotence and Eighth Symposium on Corpus Cavernosum Revascularization, Milan, Italy. Contact: Organizing Secretariat, OMNIA Meeting and Congressi, Via Senato 18, 20121 Milan, Italy.
October 9–10	BAUS Autumn Meeting, Swansea. Contact BAUS Office.

British Journal of Urology (1991), 68, 670–671

Book Reviews

Sexology. Edited by W. Eicher and G. Kockott. Pp. xiii+403. Berlin, Heidelberg, New York, London, Paris, Tokyo: Springer-Verlag. 1988. Price: DM 178,00.

This book is the Proceedings of the 1987 Eighth World Congress for Sexology which took place in Heidelberg. The subjects covered include family planning, sterility and sexuality, erectile dysfunction, sexuality in the elderly and in marriage, trans-sexualism, sexual therapy, sexuality and illness, sexuality and the handicapped, and AIDS.

There are many interesting contributions under these headings. The contributions are both of the medical and social nature. Sometimes they are anecdotal. It is doubtful whether this book would be of great use to many practising urologists but for those who have a special interest in human sexuality there are many interesting items to be found.

Renal Disease in Children. Clinical Evaluation and Diagnosis. Edited by A. Y. Barakat. Pp. xviii+514. New York, Berlin, Heidelberg, London, Paris, Tokyo, Hong Kong: Springer-Verlag. 1990. Price: DM 140,00.

This is an interesting and practical book which should be on the library shelves of adult and paediatric renal units and in general paediatric wards. It is an easy book to read and is well set out; there is a good index, so that finding the relevant chapter or section of the chapter is simple. The text is well supplemented with tables and diagrams and fulfils its aim of providing a compendium on the clinical evaluation of renal disease in children.

Paediatric nephrology has advanced enormously in recent years and this is the only book that provides a practical guide to the clinical investigation of kidney disease in children. It avoids extensive discussion of disease mechanisms, pathophysiology and therapy. Although a multi-author volume, it has been edited well and unnecessary overlap and duplication have been minimised. It is concise, which is a boon to busy house staff. Its clear and refreshing practical approach, without sacrificing a degree of scholarship, is a testament to editorial skills. The book follows a logical progression from the general examination of the child and the urinary sediment to the special problems of early diagnosis and intervention in the prevention of kidney disease. There is a superb collection of reference intervals, formulas, nomograms and curves which are so essential in paediatric practice.

The last appendix, which lists the conditions and syndromes associated with renal abnormalities, will delight those who like to collect this information and is a blessing for those of us who need to look it up.

Neurobiology of Incontinence. (Ciba Foundation Symposium 151). Pp. ix+336. Chichester, New York, Brisbane, Toronto, Singapore: Wiley. 1990. Price: £35.95.

This addition to the Ciba Foundation Symposia series enters a market that already seems saturated with other informative texts. However, this book merits special attention, being the first publication of its kind not only to try to bridge the gap between basic scientists and clinicians but also to consider all types of incontinence, both urinary and faecal.

There are authoritative chapters by undoubted world experts on the neuroanatomy, physiology and pharmacology of both excretory functions and the assessment and management of the associated clinical problems. Over 100 pages are assigned to a transcript of the lengthy discussions which followed on the day. These are compelling reading for anyone interested in this subject and must provoke enough ideas for the basis of a few theses!

Though somewhat expensive, the book will be a valuable resource and is likely to be read more than once by at least one reader It lends weighty support to the philosophy of developing multidisciplinary units, including gynaecologists, proctologists and urologists as well as basic scientists, physiologists and nurses, to deal with all disorders of evacuation and the pelvic floor.

Micturition. Edited by J. O. Drife, P. Hilton and S. L. Stanton. Pp. xiii+356. London, Berlin, Heidelberg, New York, Paris, Tokyo, Hong Kong: Springer-Verlag. 1990. Price: DM 180,-.

This book was developed from an RCOG Study Group held in October 1989. The participants included urological and colorectal surgeons, a neurologist as well as scientists and gynaecologists. The subject matter is covered in 6 sections: basic science, investigation, voiding difficulties, genuine stress incontinence, detrusor instability and prolapse and alimentary tract A mild criticism of this very well presented book is the title: while the first 2 sections cover the basis of micturition, the main purpose of the book is to examine *disorders* of micturition. The multidisciplinary presentation of this topic once again emphasises the need for training and experience in problems of disordered micturition so that accurate diagnoses and optimum treatment are achieved. This book will have appeal to a wider readership and is highly recommended.

How to get Equipment for Disability. Compiled by M. Mandelstam. Pp. xx+501. London: Jessica Kingsley Publishers and Kogan Page for The Disabled Living Foundation. 1990. Price: £12.95.

The Disabled Living Foundation is a national charity that provides practical, up-to-date advice and information on all aspects of living with disability for disabled people and their carers. In addition to these services, the Foundation has a reference library, publishes books and resource papers and offers conferences and training for both professional and voluntary sector workers. This book is an impressive compilation of information on almost every conceivable aspect of funding and finding equipment for disability. A unique reference source.

The Management of Male Infertility. Edited by T. B. Hargreave and T. E. Soon. Pp. ix+258. Singapore, Hong Kong, New Delhi, Auckland, Boston: P G Publishing. 1990. Price: US$35.00.

This 250-page book is possibly the best buy on this subject in the English literature. It is based on a series of lectures given at a Symposium in Singapore in the autumn of 1988. The theme of the whole book is practical guidance on the current management of male infertility. The authors draw on a wealth of experience and include important data from the WHO Manual of Semen Analysis and the WHO standardised investigation of the infertile couple. While it may be true that this book should be regarded as a companion to other texts on the subject it gives an excellent distillation of current thinking on all aspects of male infertility, together with an important chapter on the investigation of the female partner. The authors set out to give a critical approach that will help towards maintaining cost effectiveness and critical use of limited resources. These objectives are easily achieved and this book is by far the best value for money on the management of male infertility.

Lasers in Urology. Principles and Practice. (The Bloomsbury Series in Clinical Science). Edited by T. A. McNicholas. Pp. 168. London, Berlin, Heidelberg, New York, Paris, Tokyo, Hong Kong: Springer-Verlag. 1990. Price: DM 178,00.

This is a very well produced book that gathers together expertise from the Institute of Urology and from the National Medical Laser Centre, London. The contents are systematic, beginning with an introduction to lasers and laser physics, then laser treatment of urological conditions and concluding with the future of lasers in urology. The experience described in this book is encouraging, but many urologists will want to see more data that show improved quality, reliability, safety and especially cost effectiveness. This is an important development in urology and this state-of-the-art book is recommended.

CT and MRI of the Genitourinary Tract. Contemporary Issues in Computed Tomography, Volume 13. Edited by S. M. Goldman and Olga M. B. Gatewood. Pp. xiv+323. New York, Edinburgh, London, Melbourne: Churchill Livingstone. 1990. Price: £59.50.

This book is number 13 in a series entitled Contemporary Issues in Computed Tomography The editors are the Professor and Associate Professor in the Departments of Radiology and Urology at The Johns Hopkins School of Medicine, Baltimore. This is a comprehensive text that gives an excellent guide to the current roles of both CT and MRI in evaluating the urinary tract, including the adrenal gland. Almost all of the chapters conclude with an authoritative summary or choice of modality. It is acknowledged that only limited experience with MRI has been reported in some of the diseases and organ sites and it is also acknowledged that proper and cost-effective use of these methods depends on the understanding of when and how to use them in relation to other diagnostic methods. This then is the main disadvantage of this type of book—the text is clear, the illustrations very well presented—but—could the information have been gained by other more available methods? It is inevitable that until a good base of experience is available with these new methods of imaging, then some of the questions cannot be answered, but clinicians will look forward to another volume in this series that addresses the subject of cost effectiveness of all imaging methods in the urinary tract.

British Journal of Urology (1991), **68**, 672

Erratum

re **A Consumer's Guide to Commercially Available Urodynamic Equipment.** D. G. Barnes, D. Ralph, P. D. Hill, C. A. Lewis, P. J. R. Shaw and P. H. L. Worth.
Br J Urol (1991), **68**, 138–143

The Editor and publishers wish to apologise for having omitted the name of the third author, P. D. Hill, from the list of authors of the above article. We are sorry for the inconvenience that this has caused.

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